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PORTAL CIRRHOSIS

CLINICAL AND PATHOLOGIC REVIEW OF 782 CASES FROM 16,600 NECROPSIES *

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Despite the voluminous literature on Laennec's cirrhosis, there are still many unanswered questions about this disease. In the hope of solving some of these problems, this study was undertaken. The incidence of cirrhosis of the liver, especially of the type usually associated with chronic alcoholism, is relatively high at the Los Angeles County Hospital. Although the percentage of cases necropsied with this diagnosis varies from time to time, during the past several years it has averaged about 5 per cent. The so-called subacute phase[1,2] appears to be extraordinarily frequent in this area, with probably the highest incidence of any comparable area in the United States. A moderate number of patients who acquire this type of cirrhosis are Mexicans or persons of Mexican descent. These individuals drink wine chiefly, while some drink wine plus beer or whisky, or both. They prefer sweet wine and commonly drink about 2 quarts daily if they drink only wine. The relatively large Mexican population is one factor that makes subacute cirrhosis so common in Los Angeles County. The major factor lies elsewhere, however, since the Mexicans in this study amounted to only 20 per cent while 74 per cent were non-Mexican white Americans.

It was hoped that a large series of this kind would help clarify the relationship of alcoholic consumption and dietary deficiency factors to portal cirrhosis. Very early in the study, however, it was realized that too little data had been recorded in the patients' charts as to the amount and kind of alcoholic beverages used and that deplorably little

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data were available on the amount and quality of the diet. The clinician in the group (A.Y.O.) therefore undertook a separate study of the effects of dietary deficiency. The study by Olsen[3] included 100 living patients in the Los Angeles County Hospital with the diagnosis of portal cirrhosis, who were interviewed regarding dietary factors and drinking habits. Two different groups of 100 non-cirrhotic patients were likewise interviewed to serve as controls. One of these groups was in the Los Angeles County Hospital; the other was from Dr. Olsen's private practice.

It is commonly believed that persons with chronic alcoholism have less coronary disease and that the arteries generally exhibit less arteriosclerosis than is seen in the general population. It was anticipated that a large series of cases might provide the answer, or at least approach the truth more closely than had been possible heretofore.

Related closely to the question of arteriosclerosis is the incidence of hypertension in chronic alcoholic patients with cirrhosis. If there is less coronary sclerosis and less general arteriosclerosis, there should be less hypertension.

Another objective was to determine the relation of hepatic changes to jaundice in patients with cirrhosis. Many patients in the subacute stage of cirrhosis enter the hospital with jaundice or they develop jaundice soon after reaching the hospital. A goodly percentage of these patients die. Does the liver in these particular patients reveal changes that explain the presence of jaundice? Besides these fairly definite objectives, a natural curiosity existed in our minds as to minor factors that might come to light when a large series of cirrhotic patients was studied.

Methods of Study

All cases of portal cirrhosis were analyzed from about 16,600 necropsies. Mimeographed outlines were prepared calling for pertinent clinical and laboratory data, kinds and amounts of alcoholic beverages consumed, kind and quality of diet. Space was provided for gross and microscopic descriptions of the liver and for causes of death.

This material, except for the histologic description of the liver, was obtained from the hospital charts which included the necropsy records. One of us (E. M. H.) has studied the liver sections from all cases in which microscopic slides were available. Slides of the liver were missing from only 30 cases. Since it was planned to have the data put on punch cards and segregated by means of the Holerith machine, the histologic description was expressed in the following manner.

Portal fibrosis: 1=minimal, 2=moderate, 3=advanced, 4=far advanced. The varying degrees of bile duct proliferation, round cell infiltration of connective tissue, fatty infiltration of hepatic cells, and necrosis of hepatic cells also were each expressed as 1, 2, 3, and 4 plus. For liver cell hyperplasia 5 plus was added to indicate hepatoma or primary tumor of the liver. This form proved to be adequate, but paucity of data on many of the charts made the material in these instances rather sketchy. This was true of the clinical features and clinical laboratory findings. Much of this had been unavoidable owing to death of the patient before proper work-up could be accomplished.

Definitions of Terms

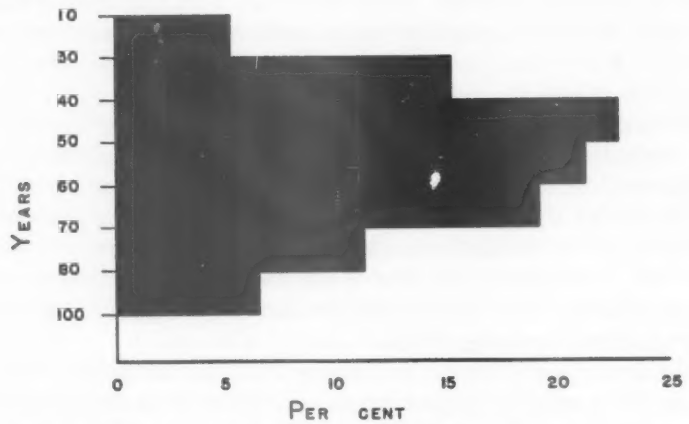
Subacute portal cirrhosis or subacute alcoholic cirrhosis refers to the early hypertrophic fatty stage of portal cirrhosis. The liver is large, weighing 2,000 to 5,000 gm., the surface smooth or granular, but not hobnailed (Figs. 1 and 2). The amount of fibrosis is minimal to moderate, fatty infiltration is moderate to marked, often with focal necrosis. Liver cell regeneration is minimal. It is sometimes referred to as subacute alcoholic cirrhosis because almost without exception these patients are heavy drinkers.

Subchronic portal cirrhosis (Laennec's) is the convenient designation we have assigned to the stage of cirrhosis between the large, fatty subacute phase and the small, atrophic hobnail variety (Figs. 3 and 4). These livers vary in size from normal to moderately large (1,400 to 3,000 gm.). The surfaces are coarsely granular to nodular. Fatty infiltration varies from minimal to moderate (1 to 2 plus), while portal fibrosis varies from moderate to severe. Regeneration of liver cells is of moderate degree.

Atrophic portal cirrhosis (Laennec's) is the ordinary small hobnail liver weighing 900 to 1,400 gm. (Figs. 5 and 6). There is little or no fat; portal fibrosis is marked with perilobular bands surrounding rounded masses of regenerating liver cells. Fibrous tissue proliferation is no longer active, causing the liver to have a healed appearance microscopically.

Atypical cirrhosis. There were 32 cases, from 782, which failed to qualify histologically as portal cirrhosis and were designated atypical cirrhosis. In a number of instances the clinical picture, likewise, did not conform. Thirty-one per cent of these patients died of cardiac failure (Table V). This is twice the percentage of those of the atrophic cirrhotic group who died of congestive failure. The percentage of deaths from arteriosclerosis, including encephalomalacia, was

6.25. This, likewise, is twice as high as in any other cirrhotic group. Of the atypical group, 9.37 per cent died of malignant neoplasia, and 9.37 per cent died of miscellaneous causes. The incidence in these two groups is also considerably higher than in the cirrhotic subgroups. Although these 32 cases were diagnosed as cases of Laennec's cirrhosis following necropsy, they apparently were a heterogeneous class, as the above data indicate. The largest group probably belonged under congestive cirrhosis.



Text-fig. 1. Graph showing age distribution, by percentage, of 782 persons dying of Laennec's cirrhosis.

CLINICAL DATA

Age (Text-fig. 1). The ages ranged from 10 to 90 years. Almost half (49 per cent) of the cases occurred between 40 and 60 years, 17 per cent before 40, and 34 per cent after 60 years. Fifty per cent of both the subacute and subchronic cases occurred between 40 and 60 years of age; 80 per cent of the atrophic cases occurred after 50 years, the greatest incidence being above 60 years.

Sex. In the Los Angeles County Hospital there is an excess of males over females in the necropsy population, males forming about 61 per cent. It will be noted in Table I that among the cirrhotic patients necropsied the excess of males over females was even greater, amounting to 68 per cent of the entire group.

Race. A study of race is important in cirrhosis because of differences in habits and susceptibilities. In India, where Laennec's cirrhosis is common, deficiencies due to poorly balanced diets and insufficient quantity of food are the chief etiologic factors.[4] Alcoholism is rare

among the people of India. In some parts of the Orient parasitic infestation of the liver is the chief cause of cirrhosis. In Southern California the relatively large Mexican population constitutes a factor since these people drink considerable quantities of sweet wine.

In Text-figure 2 it is demonstrated that the Mexican group makes up

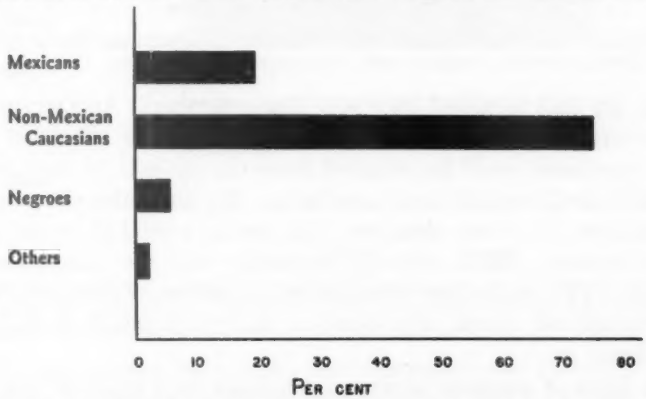
TABLE I

Number of Male and Female Cirrhotic Patients in the Series Compared with the Total Number of Necropsies (16,600)

	Male	Female	Total	Male, per cent
Cirrhosis	530	252	782	68
No cirrhosis	9.649	6,169	15,818	61
Total	10,179	6,421	16,600	

20 per cent of our cirrhotic patients, non-Mexican Caucasians about 74 per cent, Negroes 4 per cent, and other races 2 per cent.

Habitus. Weights of approximately 50 per cent of the patients were increased an estimated 5 to 10 lbs. because of edema and ascites. In spite of the increase in weight due to excess fluids, only 6 per cent weighed over 176 lbs. while 43 per cent weighed less than 110 lbs.

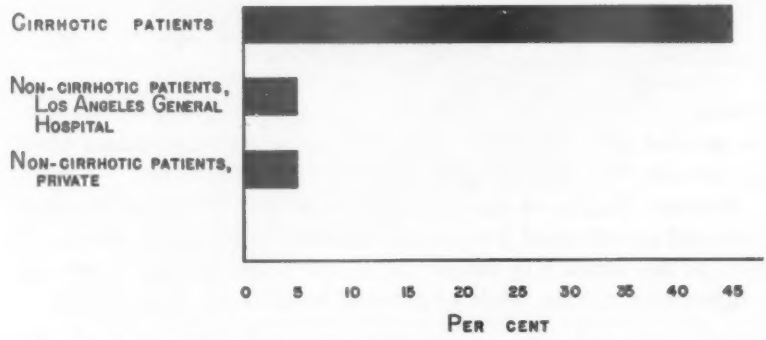


Text-fig. 2. Graph illustrating distribution, by percentage, of races in a large series dying of Laennec's cirrhosis.

Diet (Text-fig. 3). In approximately 80 per cent of the histories there was no record of diet. When any statement was made, it was a general one, such as "diet poor" or "diet poor when drinking" without any effort to elaborate on the type or amount of dietary intake. In 19 per cent the diet was recorded as "poor." Dietary histories were not obtained for disoriented and comatose patients. Assuming the diet

was equally poor in such individuals, a corrected total of 50 per cent dietary deficiency is found. This is low compared with 64 per cent deficiencies found in an interview with 100 living cirrhotic patients.[8] In the latter it was significant that protein was deficient in 45 per cent of patients and B-complex in 60 per cent.

Kinds and Quantity of Alcohol Consumed. It is practically impossible to obtain accurate data on the quantity of alcohol consumed by any group of patients. About 3 per cent of our group claimed to be light drinkers, 11 per cent stated they were moderate drinkers,



Text-fig. 3. Graph illustrating percentage of patients with protein and vitamin deficiencies in Laennec's cirrhosis, compared with a non-cirrhotic control group.

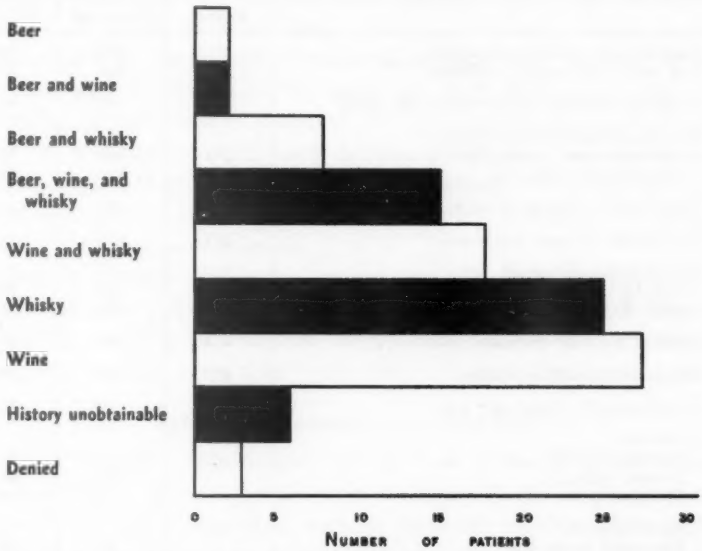
and 50 per cent admitted they were heavy drinkers. Another 29 per cent entered the hospital in a disoriented or comatose condition. No direct statement could be obtained from the patients of this group, but their condition indicated intoxication. We have, therefore, added this group to the heavy drinkers. This makes a total of 79 per cent heavy drinkers, which compares favorably with the data of other workers.[3] The percentages reported are as follows: Patek and Post,[5] 54; Ratnoff and Patek,[6] 87; Patek *et al.*,[7] 77; Kimball, *et al.*,[8] 79; and Olsen,[3] 92.

The kinds of alcoholic beverages consumed by a group of 100 cirrhotic patients interviewed at the Los Angeles County Hospital are illustrated in Text-figure 4, which is copied from Olsen's report. Wine ranked first, with 28 per cent of the group drinking wine only. As stated previously, this was usually sweet wine, muscatel probably ranking as first choice. Those who drank wine only, commonly consumed about 2 quarts daily. This amount provides about 1,500 calories. Whisky ranked second, with 25 per cent of the group preferring this drink

alone. Seventeen per cent used wine and whisky, 15 per cent beer, wine, and whisky, while only 8 per cent used beer and whisky. Only 2 to 3 per cent used beer and wine, or beer alone.

SYMPTOMS AND SIGNS

Symptoms complained of prior to the terminal stages were mainly those of dyspepsia and, in those patients with ascites, a sense of fullness. The major signs were ascites, edema, jaundice, hepatomegaly, splenomegaly, telangiectasis, hematemesis, dermatitis, and disorientation.



Text-fig. 4. Graph depicting kinds and relative amounts of alcoholic beverages consumed by 100 patients with Laennec's cirrhosis. (Reproduced by permission from *The American Journal of Medical Sciences*, 1950, 220, 478.)

A great number of patients had voluminous out-patient histories, with consultations and laboratory tests over a period of years. These patients with vague symptoms were often treated as neuropsychiatric cases, and were shunted from one clinic to another, with extensive laboratory work ordered. When liver function tests were done during these early stages, they usually presented normal values. They could not be depended upon to show early liver damage. Because of normal liver function tests the impression of liver disturbance was often dropped and the patient again was sent on a round of various consultations

until the terminal stage became manifest with the development of major signs such as jaundice, edema, ascites, hemorrhage, or hepatomegaly.

After reviewing these charts, one must conclude that more attention should be paid to the mild gastro-intestinal symptoms of patients and a more detailed inventory made of their dietary habits while thinking in terms of alcoholism and cirrhosis. One must be on the alert for the minor signs, such as slight liver enlargement, spider angiomata, palmar

TABLE II
Summary of Laboratory Data (782 Cases)

	No. tests	No. altered	Per cent
Anemia (hemoglobin under 80%)	387	280	72
Red blood cells (under 4 millions)	312	231	74
Leukocytosis (over 10,000 without infection)	398	66	17
Albumin-globulin ratio reversed			
Albumin under 3.5 gm. %	361	320	89
Globulin over 3 gm. %	361	239	66
Total proteins decreased below 6 gm. %	361	189	51
Non-protein nitrogen increased	403	208	52
Icterus indices increased	312		
over 15		236	76
over 8		289	93
Prothrombin time decreased under 70%	208	200	96
Wassermann reaction positive	455	74	16
Urobilinogen increased over 1-20	24	18	75
Cholesterol	111		
Decreased (under 150)		34	30
Normal (150-275)		67	60
Increased (over 275)		10	9
Cholesterol esters	71		
Decreased (under 60)		41	58
Normal (over 60)		30	42

erythema, gynecomastia, and evidences of nutritional deficiencies. Normal liver function tests should not guide our thinking. It is at this time that an insidious progressive process may best be treated and arrested. Waiting until one of the major signs appears, too frequently means being able to give only partial relief and comfort for the last few months of life.

Many patients died of pneumonia and other infections without showing leukocytosis (Table II). Seventeen per cent of the patients showed leukocytosis unassociated with infection, hemorrhage, or other arrested. Waiting until one of the major sings appears, too frequently variably were associated with necrosis of the liver. Analysis of the

type of cirrhosis associated with leukocytosis showed subacute, 23 per cent; subchronic, 12 per cent; atrophic, 14 per cent; and atypical, 18 per cent.

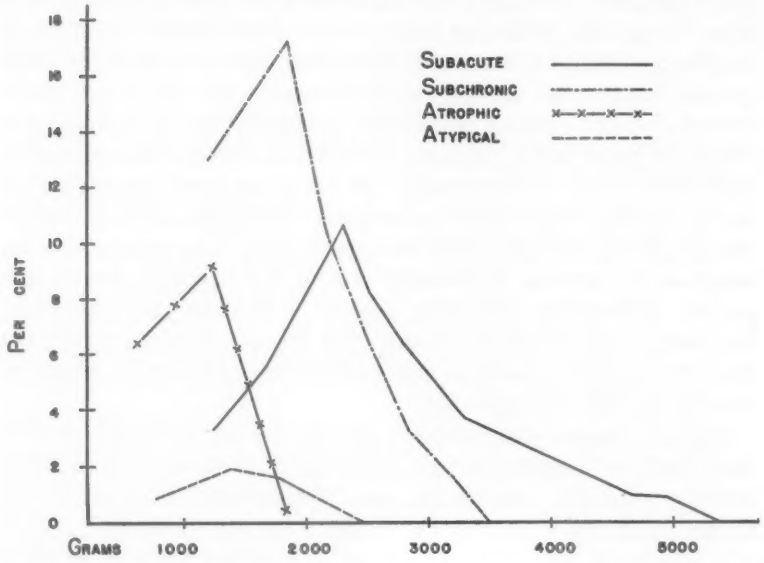
Non-protein nitrogen determinations were done on 403 patients (51.53 per cent). There was an elevation above normal in 208 patients (51.6 per cent). Of these, 107 (26.6 per cent) were associated with liver cell necrosis, while 105 cases (26 per cent) showed elevation in the absence of liver cell necrosis. Conversely, of the 195 patients with normal non-protein nitrogen determinations, 102 (25.3 per cent) showed liver cell necrosis. Deaths due to hemorrhage from esophageal varices occurred in 143 patients. Non-protein nitrogen determinations were made in 68 of these cases; 38 (55.9 per cent) were elevated above normal. Death from hemorrhage frequently occurred before the non-protein nitrogen could become elevated. Non-protein nitrogen elevation in cirrhosis is probably due to the terminal state of the patient, malnutrition with body protein breakdown, gastro-intestinal hemorrhage with blood protein digestion, secondary renal insufficiency from decreased blood volume, excess antidiuretic hormone, and hepato-renal lower nephron nephrosis.

Plasma albumin was under 3.5 gm. per 100 cc. in 89 per cent of tests made and globulin over 3 gm. per 100 cc. in 66 per cent. Thymol turbidity, cephalin flocculation, and bromsulfalein tests were performed in so few cases that the results were not significant.

PATHOLOGIC ANATOMY OF THE LIVER

Gross Features. The surface of the liver in portal cirrhosis may be described as smooth, granular, or nodular. In the early phases of subacute cirrhosis the surface may be perfectly smooth. Some of the larger livers, weighing 5,000 to 6,000 gm., usually were smooth and yellow or gray-yellow. At times the color was a deeper orange-yellow due to jaundice. Our data on the liver surface changes are inaccurate because the resident pathologists failed to distinguish between granular and nodular liver surfaces. Many of the granular surfaces were described as nodular. The subacute cases should fall, with few exceptions, into the *smooth* and *granular* columns. The cases of subchronic cirrhosis should have the largest number in the *granular* column with almost equal numbers in the *smooth* and *nodular* groups. Atrophic cirrhosis is the typical *hobnail* nodular type of liver. A few of these will be coarsely granular and a very few may show only slight unevenness with some wrinkling or fissuring. The small size and marked firmness leave little doubt as to the underlying condition.

Liver Size. Text-figure 5 shows that the widest range of liver size as well as the largest cirrhotic livers were in the subacute group. The extremes ranged from around 1,500 gm. to over 5,000 gm. The largest number of cases fell in the 2,000 to 3,500 gm. category. The subchronic cases ran from 1,500 to 3,500 gm., with the largest number

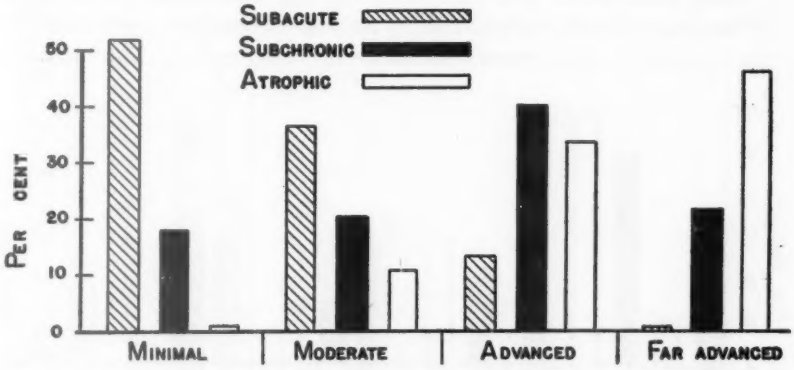


Text-fig. 5. Graph showing the percentage distribution of livers as to size in 750 patients dying in various stages of cirrhosis.

occurring in the 1,800 to 2,500 gm. group. The atrophic cirrhotic group began at 900 gm. and went to 1,800 gm., with the mean at about 1,250 gm.

Periportal Fibrosis. It is evident from Text-figure 6 that periportal fibrosis was minimal to moderate in the *subacute* cases. There is a sharply sloping curve from the high of 51 per cent showing minimal fibrosis to 35 per cent in the moderate group. Only 13 per cent showed more advanced fibrosis of periportal and perilobular distribution. A few cases were included in the subacute group that had very slight increase in connective tissue of the portal areas. One might question whether these cases were properly included in the category of cirrhosis. On the other hand, these patients had all the signs and symptoms of early cirrhosis, with a fatty liver, often focal hepatic necrosis, and jaundice. They were all chronically alcoholic. The *subchronic* cases fell mainly between the subacute and atrophic groups with the largest

number showing advanced portal cirrhosis. Lines drawn from the tops of the columns (Text-fig. 6) form a normal curve. About 16 per cent were in the minimal, 20 per cent in the moderate, and 40 per cent in the advanced group, dropping to 20 per cent in the far advanced group. These are the large granular livers that are often somewhat fatty. The connective tissue varied from cellular to fairly dense. Perilobular fibrosis was usually well developed. As expected, the *atrophic* livers showed the most advanced periportal fibrosis. Only 10 per cent were in the moderate group, 33 per cent in the advanced,



Text-fig. 6. Graph illustrative of the percentage incidence of minimal, moderate, advanced, and far advanced periportal fibrosis in the three phases of Laennec's cirrhosis.

and 46 per cent in the far advanced category. The fibrous tissue in this group was usually dense and showed collagen formation. The hepatic lesion appeared to be healed and relatively inactive. Perilobular fibrosis was prominent, tending to surround pseudo-lobules of regenerating liver cells.

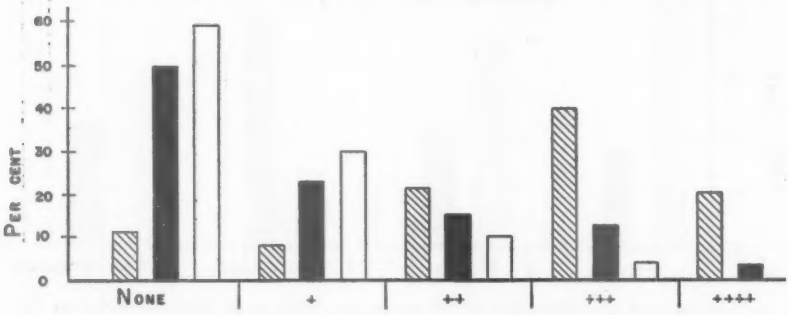
The assignment of a given case of cirrhosis to one of the three groups depends upon a number of factors. While the degree of fibrosis is important, the immaturity or maturity of the connective tissue is significant, since maturity tends to increase from the subacute to the atrophic stage. Other factors are size of liver, probably as important as the degree of fibrosis; nature of liver surface; presence and amount of fatty infiltration; presence or absence of necrosis; and degree of liver cell degeneration.

New Bile Ducts. There seemed to be no significant difference in the number of proliferating bile ducts in the various types of cirrhosis. This feature may be of some help in differentiating biliary and portal cirrhosis but is not helpful in separating the various stages of the

latter. New bile ducts are prominent in the healing phases of acute hepatitis and in portal cirrhosis without regard to stage.

Round Cell Infiltration. From one fifth to one fourth of the cirrhotic livers of various types showed little or no round cell infiltration. The subacute group exhibited the least with its highest percentage of involvement in the 1 plus column. The subchronic showed more cases falling in the 2 and 3 plus columns, while the atrophic group showed a fairly uniform percentage in all three categories. The heaviest round cell infiltration was therefore in the atrophic group.

Fatty Infiltration. The subacute group by definition includes most of the patients with fatty cirrhosis, the high percentages occurring in the 2, 3, and 4 plus columns as shown in Text-figure 7. The highest



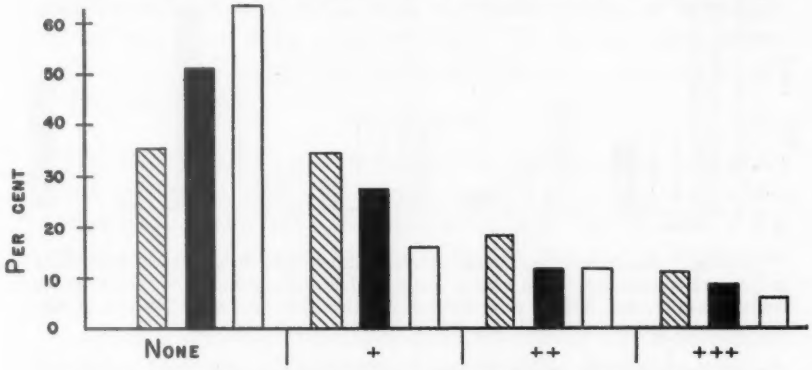
Text-fig. 7. Graph illustrative of the percentage incidence of the five grades of fatty infiltration in the various phases of Laennec's cirrhosis. Key is the same as for Text-figure 6.

percentage, 39.29, was in the 3 plus column. Only 12.06 per cent of the livers in this category were free of fat. In the subchronic class 50.13 per cent contained no fat and 23.57 per cent, 1 plus fat, while the percentage fell off rapidly in the higher degrees. Nearly 60 per cent of the atrophic group contained no fat, almost 30 per cent showed only 1 plus, and only 8 per cent contained 2 plus fat. Hartroft and Sellers[9] have contended that part of the fat in cirrhosis is found in small cysts formed by the confluence of several fatty liver cells. The nuclei of the involved cells become arranged in a bead-like pattern about the small cysts. Hepatic cells average about 14 μ in diameter while the fatty cysts may reach 50 to 100 μ. These cysts make it possible for the liver to store a greater amount of fat within a given space.

Chaikoff, Connor, and Biskind[10] produced cirrhosis with fatty infiltration of the liver in dogs maintained for a long period after depancreatization plus insulin. Later Chaikoff *et al.*[11] produced cir-

rhosis in normal dogs by prolonged feeding of a high fat diet. They concluded that continued fatty infiltration of the liver is an important causative factor in the production of cirrhosis. Best, Hartroft, Lucas, and Redout[12] have shown that sugar or alcohol added to a marginal diet (low proteins, high carbohydrates with insufficient choline) produced fatty liver and pre-cirrhotic changes in white rats. These alterations were prevented when adequate choline was fed. Alcohol or sugar when taken in excess supplants choline-containing foodstuffs and at the same time, by increasing the caloric intake, augments the demand for lipotropic agents.

It has been shown by a number of investigators of experimental



Text-fig. 8. Graph illustrative of the percentage incidence of the four grades of necrosis of hepatic cells in the various stages of Laennec's cirrhosis. Key is the same as for Text-figure 6.

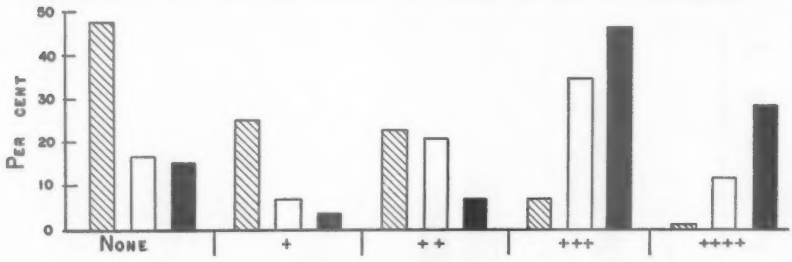
cirrhosis in white rats and other laboratory animals by means of dietary deficiency, essentially choline-poor diets, that fatty infiltration and enlargement of the liver precede the development of cirrhosis.[13-15] This appears to be the course of events in man as well. In fact, Wood and his associates[16] observed the stages in the progression of the fatty liver toward portal cirrhosis in a group of malnourished patients by aspiration biopsy. This view is favored by Hartroft[17] also. He found fibrosis beginning about the fatty cysts as their volume diminished due to leakage of their fatty contents into hepatic sinusoids and bile capillaries.

Necrosis of Liver Tissue. One third of the patients with subacute cirrhosis had no hepatic necrosis while slightly more than half of the subchronic cases and two thirds of the atrophic group were free of necrosis (Text-fig. 8). As we expected, the subacute group led in the second, third, and fourth categories, the 1 plus column being the

highest. The graph shows more necrosis in the atrophic cirrhotic livers than we had expected. The atypical cases seemed to align themselves with the subacute and atrophic groups.

There is a rough correlation between the degree of jaundice and the extent of necrosis. Patients that have 1 plus and 2 plus necrosis usually have slightly to moderately increased icterus indices. Those which have 3 plus necrosis in the microscopic sections of liver are likely to have been classified clinically as having hepatic necrosis.

Hyperplasia of Liver Cells (Text-fig. 9). Regenerative hyperplasia of liver cells was minimal in the subacute group, 44.35 per cent show-



Text-fig. 9. Graph depicting the percentage incidence of the five grades of hyperplasia or liver cell regeneration in the various phases of Laennec's cirrhosis. In this graph the cross-hatched columns indicate percentages of subacute cases; the white columns, of subchronic cases; and the solid black columns, of cases of atrophic cirrhosis.

ing no hyperplasia, while 27 per cent showed 1 plus, and 22.56 per cent showed 2 plus hyperplasia. Only a few, 6.22 per cent, were in the 3 plus column, one in the 4 plus, and none in the 5 plus columns. Regenerative hyperplasia was characteristic of the subchronic and atrophic groups; both were low in the 1 plus column but the incidence increased markedly in the 2 plus and 3 plus columns. As would be expected, the atrophic group was well represented in the 4 plus column with an incidence of 29.72 per cent.

Primary Carcinoma of Liver. Edmondson and Steiner,[17a] studying hepatic cancer in the same 16,600 necropsies studied by us, found 21 cases of primary carcinoma of the liver. These occurred among the 480 livers classified as occurring in the chronic stages, amounting to 4.3 per cent of that group. These percentages indicate general agreement with the marked degree of liver cell hyperplasia seen in the more advanced stages of cirrhosis. While the more active phases, such as may be seen in the subacute stage, are now quiescent, hyperplasia is still active. This is evident by the presence of hobnail nodules which are

characteristic of the atrophic stage. This is apparently an attempt to compensate for loss of liver parenchyma, since in this stage the liver may weigh only one half to two thirds of the normal. Much non-functioning fibrous tissue is present and the efficiency of the regenerated liver tissue is questionable. To state that hyperplasia of liver cells is a forerunner of hepatic cancer is only to repeat what is known for cancer of the breast, uterus, colon, and some other organs. No doubt the duration of the cirrhotic process and age of the patient are important, since most hepatic cancers occurred in late stages and in the older individuals.

Of the 21 cases of hepatic carcinoma reported by Edmondson and Steiner,[17a] nearly all were in males, the corrected ratio as to sex being approximately 16 to 1, while cases of hepatic carcinoma in non-cirrhotics were about equal in the two sexes. The factors which protect cirrhotic women from developing hepatic cancer are unknown, but are probably hormonal.

Size of Spleen

Very few conclusions can be drawn from the data on the size of the spleen in portal cirrhosis. A greater number of spleens were within normal limits in the subacute group in spite of the fact that a few became very large as seen in Table III, 8.56 per cent weighing over

TABLE III
Size of Spleen

Gm.	0–199	200–299	300–399	400–499	500+
	%	%	%	%	%
Subacute	41.63	26.06	17.11	4.66	8.56
Subchronic	24.92	31.47	16.25	12.19	11.65
Atrophic	30.62	30.62	14.40	13.50	9.00
Atypical	25.00	34.37	18.75	3.12	18.75

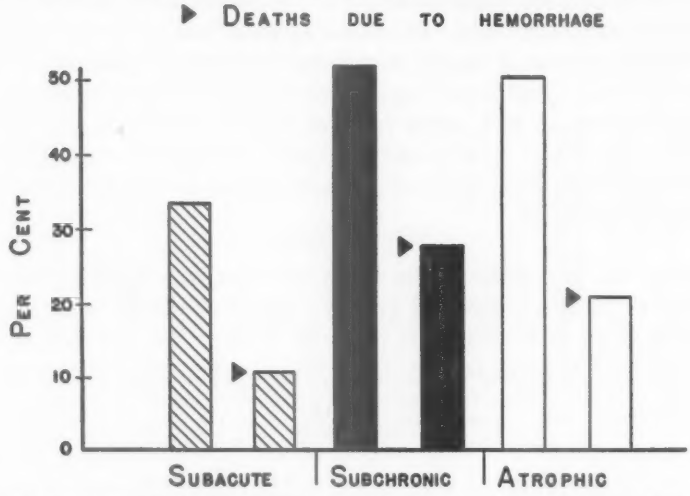
500 gm. The main conclusion is that the spleen is enlarged in all stages of cirrhosis in about 65 per cent of cases.

Esophageal Varices

It is to be expected that the element of time and the degree of fibrosis have much to do with the development of esophageal varices. Portal hypertension is probably the most important factor. Since we have no reliable statistics on the presence of this factor, we must rely on the other two factors mentioned. Perhaps liver size plays a part, especially in livers that weigh over 3,000 gm.

The incidence of esophageal varices was almost the same in the

subchronic and atrophic groups, 52.03 and 49.54 per cent respectively (Text-fig. 10). A much larger percentage than might be expected (34.24) was recorded for the subacute cases, with 10.11 per cent of the patients dying of hemorrhage. Of the subchronic patients, 25.47 per cent succumbed to hemorrhage as compared with 21.62 per cent of the atrophic cirrhosis patients. This made an over-all average of 19.06 per cent dying of hemorrhage into the gastro-intestinal tract.

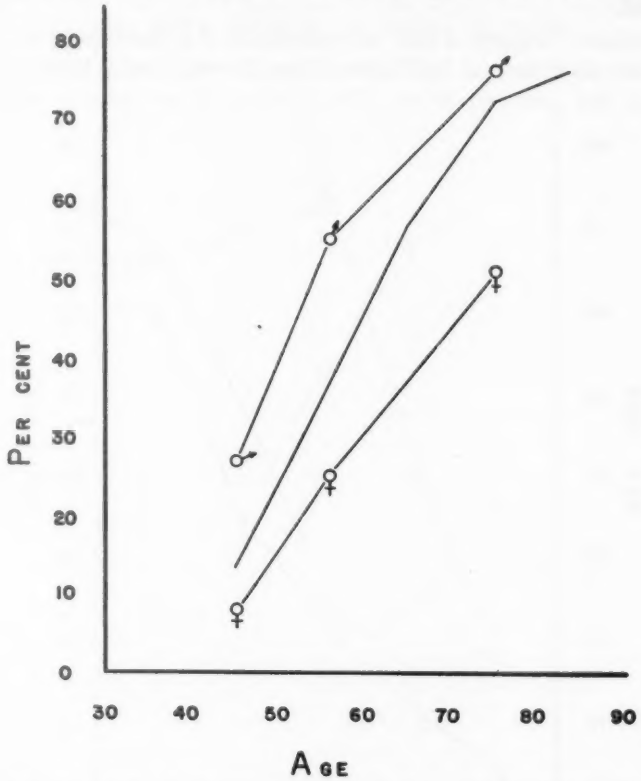


Text-fig. 10. Graph showing percentage incidences of esophageal varices and of fatal hemorrhages in the various stages of Laennec's cirrhosis.

EFFECTS OF CHRONIC ALCOHOLISM ON DEVELOPMENT OF ATHEROSCLEROSIS

There is a widespread opinion among physicians, based largely on personal experience with alcoholic patients, that alcoholism tends to spare the arteries. There are, however, few well controlled studies dealing with this subject. In our study of 782 cases of cirrhosis there was no increase in the incidence of arteriosclerosis by age groups until the eighth decade was reached. Our problem lay in finding comparable control groups for comparison with the data obtained by analysis of the cases of cirrhosis. In Text-figure 11, the graph representing the male and female controls (broken lines) is based on the study by Lake, Pratt, and Wright[18] of 536 patients in which the incidence of general arteriosclerosis is given by age groups. While cirrhotic cases were not separated as to sex, 68 per cent of the patients were males. In Text-figure 11 it is evident that the patients with cirrhosis (solid

line) fall almost midway between the male and female controls. Up to 55 years the solid line is somewhat nearer the female controls. Correcting for 32 per cent females among the cirrhotic patients would move the line to about midposition. Thus up to 55 to 60 years of age the control males averaged 8 to 10 per cent more aortic arteriosclerosis than the cirrhotic males. Since the controls come from a



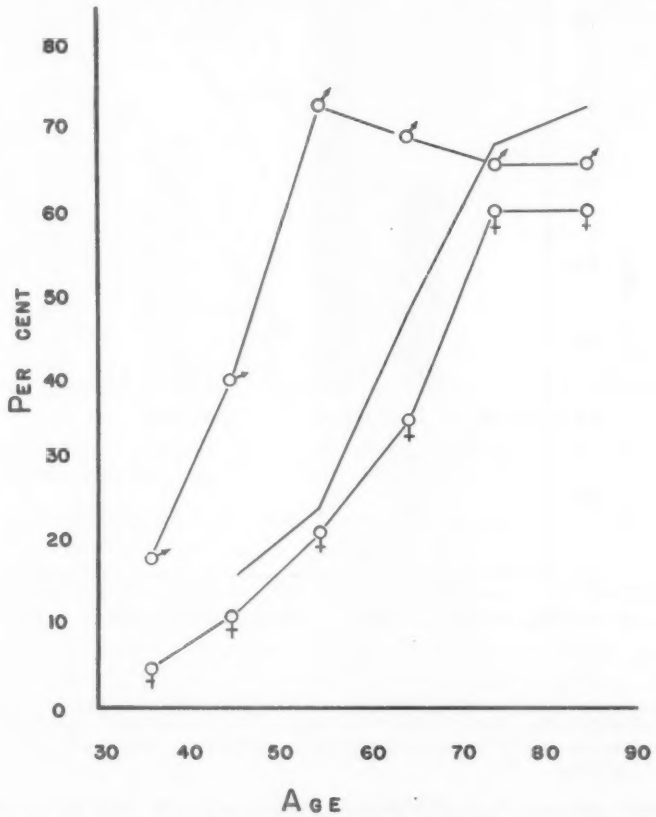
Text-fig. 11. Graph showing percentage incidence of *moderate to severe arteriosclerosis* of the aorta in patients with Laennec's cirrhosis and in control groups. Key: Lines with sex symbols are non-cirrhotic male and female controls. The center line represents the cirrhotic patients.

different area and the estimations of arteriosclerotic changes are made by different persons there is some question as to the significance of this difference.

In Text-figure 12 the incidence of coronary sclerosis is compared in the cirrhotic and non-cirrhotic groups. The control group is taken from the paper by White, Edwards, and Dry[19] for which 600 hearts

were studied, 100 in each decade from 30 to 89 years. The differences here are much more evident in the age groups up to 60 than beyond this level. At 55 years about 75 per cent of the male controls show moderate to severe coronary sclerosis while the corrected corresponding figure for the cirrhotic group (32 per cent females) would be only 30 to 35 per cent. After 65 to 70 years the differences are much less marked.

Morrison[20] suggested that atherosclerosis is a manifestation not of age but of disturbed lipid metabolism in which the liver plays a



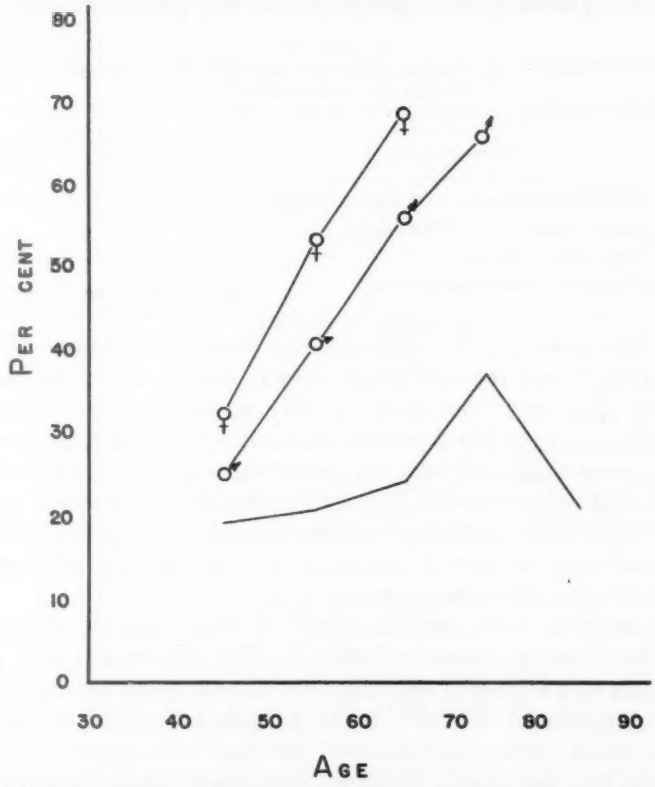
Text-fig. 12. Graph showing percentage incidence of *moderate* to *severe* coronary sclerosis in cirrhotic and non-cirrhotic patients. Key is the same as for Text-fig. 11.

significant rôle. Wolffe *et al.*[21] presented clinical and experimental data which focused attention on the liver in the atheromatous syndrome aside from the vascular phenomena. Zinn and Griffith[22] con-

cluded that there is a significant qualitative difference in the physical size of the lipid particles observed under dark field illumination of the sera of atherosclerotic and non-atherosclerotic patients and stated that cirrhosis of the liver does not influence this variation, but they suggested that the fundamental difference between arteriosclerotic and non-arteriosclerotic patients lies in the metabolic control of fat transport.

THE BLOOD PRESSURE IN PORTAL CIRRHOSIS

An opinion held generally by physicians is that reduced blood pressure is common in patients with portal cirrhosis just as it is



Text-fig. 13. Graph showing percentage incidence of hypertension in a group of 750 cirrhotic patients compared with 15,000 non-cirrhotic patients of similar ages.

believed arteriosclerosis tends to be less. Rolleston,[23] writing in Oxford Medicine, quoted from Villaret and Saint-Girons: "In portal cirrhosis, the pulse is slightly quickened, the blood pressure, both

arterial and venous, usually is low." In the 100 living cirrhotic patients interviewed by Olsen[3] only 14 per cent were hypertensive. Spatt and Rosenblatt,[24] in a study of 80 patients with portal cirrhosis, found that at the age of 60 and over, 28 per cent were hypertensive. Davis and Tanturi[25] theorized that in hepatic insufficiency the liver is unable to manufacture hypertensinogen, the precursor of angiotonin. The liver may not be able to inactivate the vasopressor material of Shorr; or an injured liver may release excess vasodepressor material. Alcohol, acting as a vasodilator, is probably a factor.

It is evident in Text-figure 13 that in cirrhotic patients there tends to be lower blood pressure than in non-cirrhotic patients of comparable

TABLE IV
Patient Groups Used in a Statistical Analysis of Blood Pressures in Cirrhotic and Non-cirrhotic Patients

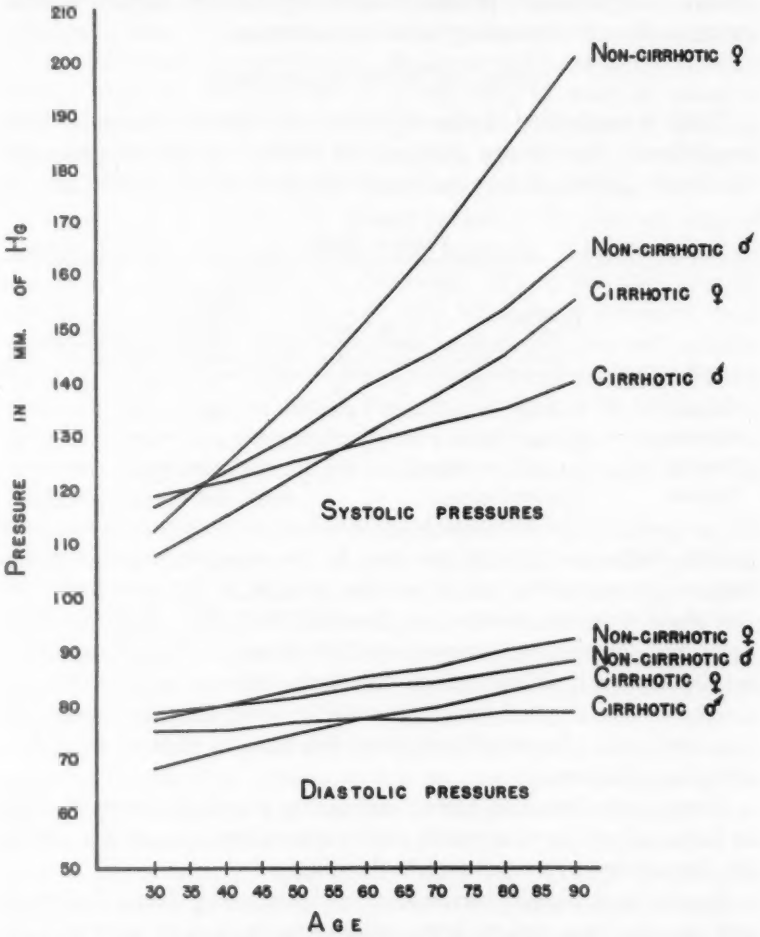
Patient groups	Number of patients	
	Male	Female
Hospital cirrhotic group (Hall, Olsen, and Davis)	470	208
Private cirrhotic group (Olsen, 1950)	54	41
Total cases of cirrhosis	524	249
Private non-cirrhotic group (Olsen)	190	305

age. The controls in this study are from the report by Master, Marks, and Dack,[26] who recorded blood pressure readings in 15,000 persons (8,483 males and 6,366 females) over 40 years of age. Assuming hypertension to be blood pressure above 150 systolic and 90 diastolic, at 60 years of age and over, the normal expectancy is 60 per cent for males and 70 per cent for females. In the cirrhotic group at age 60 only 20 per cent (males and females) showed hypertension. It would be interesting to know if confirmed alcoholic patients who are not cirrhotic show the same response.

A somewhat more detailed study* of blood pressures was made also in the groups shown in Table IV. The ages ranged from 30 to 90 years with a mean of approximately 50 years in each group. There was no significant difference in blood pressures between the two cirrhotic series (private and hospital) and they were, therefore, pooled. Within any age group, pressures were more nearly normally dis-

* We are indebted to Dr. Frederick J. Moore, Department of Experimental Medicine, University of Southern California School of Medicine, for the statistical analysis. Patients were excluded from this analysis if either the systolic or diastolic pressure was unrecorded or not clear. The group of hospital cirrhotic patients with systolic pressure under 65 or diastolic pressure under 35 were also excluded on the grounds that such pressures probably were taken in terminal shock.

tributed[27] on a geometric scale (using log pressures) than on an arithmetic scale. Log pressures appeared to be linearly related to age over the range studied. Linear regressions were therefore fitted by the method of least squares and tested for significance.



Text-fig. 14. Graph showing comparative systolic and diastolic pressures among 773 cirrhotic patients and 495 non-cirrhotic controls. This is based on data obtained in the statistical analysis by Dr. F. J. Moore.

A significant dependence of pressure on age was found with all groups except the diastolic pressure of cirrhotic males in which no significant change with age was found. The fitted curves, reconverted to arithmetic units, are shown in Text-figure 14.

At age 50 (the approximate mean age of all groups), systolic and diastolic pressures of non-cirrhotic females were higher than those of non-cirrhotic males. In the presence of cirrhosis, pressures of males were slightly but not significantly higher than of females. Both systolic and diastolic pressures were significantly higher in non-cirrhotic than in cirrhotic patients in both sexes.

CAUSES OF DEATH IN CIRRHOSIS

Table V emphasizes the importance of infection as a cause of death in cirrhosis. Nearly one third of the patients in the subacute and subchronic stages of Laennec's cirrhosis succumbed to infection. A

TABLE V
Causes of Death

	Infection, acute or chronic	Hemorrhage	Hepatic insufficiency	Chronic alcoholism	Cardiac failure	General arteriosclerosis including cerebral softening	Miscellaneous	Malignant neoplasia	Tuberculosis
	%	%	%	%	%	%	%	%	%
Subacute	32.25	10.11	22.17	4.28	12.45	2.33	1.94	3.50	6.61
Subchronic	32.52	25.47	14.09	0.54	13.00	3.25	2.71	5.14	2.98
Atrophic	35.13	21.62	13.51		15.31	2.70	0.90	6.30	4.50
Atypical	25.00	15.62			31.25	6.25	9.37	9.37	3.12

slightly higher percentage was seen in the atrophic stage, probably because these patients were in an older age group. The more important infections were the pneumonias, bronchial and lobar; pyelonephritis, acute and chronic; and streptococcal infections of pharynx and upper respiratory tract. Of the chronic infections, tuberculosis was the most common. The atypical group presented a lower infection death rate (25 per cent). Apparently many of the patients died of congestive circulatory failure.

Hemorrhage from esophageal varices was a common cause of death in the subchronic and atrophic stages, amounting to 25.47 per cent in the former and 21.62 per cent in the latter.

Death due to hepatic insufficiency, as indicated by liver cell necrosis and jaundice, was highest in the subacute group (22.17 per cent). In these patients the liver was often very large and fatty. Many of these patients were brought to the hospital following an alcoholic debauch and already were showing jaundice or they developed jaundice soon after reaching the ward. The jaundice was usually indicative of hepatic necrosis. A goodly number of these patients presumably died of hepatic insufficiency. Almost an equal number of patients in the

subchronic and atrophic phases died of this cause, 14.09 and 13.51 per cent, respectively. These figures are considerably below those for the subacute group.

A surprisingly small number of patients died of alcoholism as manifested by symptoms pertaining to the central nervous system. In the subacute group 4.28 per cent were in this category while only 0.54 per cent (2 patients) belonged to the subchronic and none to the atrophic group. Hall and Morgan,[2] in 1939, reporting 68 cases of subacute and subchronic cirrhosis, found 20 per cent of deaths due to alcoholic psychosis often associated with peripheral neuritis and/or pellagroid dermatitis, the latter conditions indicative of avitaminosis.

About 12.5 to 15 per cent of the patients with cirrhosis died of cardiac failure. The percentage rose gradually from the subacute (12.45 per cent), through the subchronic (13.00 per cent), to the atrophic group with 15.31 per cent. The latter group contained many of the older patients. Some were even in their seventies and eighties. Naturally, a greater number of these would succumb to cardiac failure. Since the percentage of deaths from cardiac failure in the atypical group is double the percentage of the atrophic group it seems likely that a considerable part of the cirrhosis in this category is of the congestive or cardiac type.

There were 6,458 deaths due to cardiovascular causes among 40,000 necropsies at Los Angeles County Hospital, which amounts to 16.145 per cent. Cardiac failure among the cirrhotic patients approached this figure very closely. The average for the three main groups was 13.58 per cent. The atrophic cirrhosis patients, with 15.31 per cent deaths due to cardiac failure, almost equalled the figure for the general necropsy population.

Deaths ascribed to general arteriosclerosis including cerebral hemorrhage and softening were very low in our three main groups of cirrhosis, ranging from 2.33 per cent in the subacute, to 3.25 per cent in the subchronic, and 2.70 per cent in the atrophic group. For the general run of necropsy cases at the Los Angeles County Hospital the corresponding percentage is 7.225. Since this figure includes infants and children, the corrected figure would probably reach at least 8.00 per cent. Again, the percentage of deaths due to arteriosclerosis in the atypical group was double that of the other cirrhotic groups. This again indicates that the atypical group was not composed primarily of patients with Laennec's cirrhosis.

The results in the column designated miscellaneous also showed that the atypical group was entirely out of line with the true cirrhotic

groups. Of the atypical cases 9.37 per cent as to cause of death fell in the miscellaneous column while the three groups of Laennec's cirrhosis ranged from 0.90 to 2.71 per cent.

The atypical group had a high percentage of deaths from malignant neoplasms (9.37 per cent). The subacute group was low (3.50 per cent) in deaths due to cancer since these patients were relatively young (30 to 55). The subchronic cases had 5.14 per cent deaths due to this cause while the atrophic group was higher with 6.30 per cent. The latter patients were largely in the high cancer-age range; also there was a greater tendency for primary liver tumors to develop in this group in which hyperplasia of liver cells was most marked.

Text-fig. 15. Graph showing percentage of deaths due to portal cirrhosis in Los Angeles County General Hospital from 1918 to 1947. Of note is the marked decrease in deaths from cirrhosis during the prohibition years, 1918–1932.

The greatest number of deaths from tuberculosis occurred among the patients with subacute cirrhosis (6.61 per cent). The reactions generally were more violent in this group, with greater stress and strain. The younger age range also definitely favored tuberculosis. The subchronic patients had less than half the proportionate number of deaths from tuberculosis as did the subacute, amounting to 2.98 per cent. Of the atrophic group 4.5 per cent and of the atypical group 3.12 per cent died of tuberculosis.

RELATIVE PERCENTAGE OF DEATHS AMONG PATIENTS WITH PORTAL CIRRHOSIS DURING THE YEARS 1918–1947

An interesting graph (Text-fig. 15) shows the percentage of cirrhotic deaths in the Los Angeles County Hospital beginning in the

year 1918 at about 2 per cent. This is the year that the War Prohibition Act was enacted, being replaced by the Volstead Act which became law in October, 1919. The sale of all beverages containing more than 0.5 of 1 per cent alcohol was prohibited, except by doctor's prescription. Prescriptions were limited to 24 per cent alcohol. It will be noted in the graph that deaths from cirrhosis began to fall immediately, dropping fairly precipitately until 1924 when the rate was less than 0.1 of 1 per cent. There was then a sharp rise during the next 2 years, reaching 0.9 per cent. It seems likely that the many bootlegging concerns that sprang up in the first few years of prohibition were responsible for this rise. In the next 2 years there was another sharp fall to about 0.4 per cent. This is not so easily explained. Beginning in 1928 the number of deaths rose progressively, reaching 1 per cent in 1932, which was the year the Volstead Act was repealed. Following this there was a steady rise to 4 per cent by 1940 with a still more abrupt increase in the next year to nearly 6 per cent. Between 1941 and 1947 the number of deaths varied between 4.2 and 5.8 per cent. There seems to be little question that prohibition had the effect of greatly reducing the number of deaths due to cirrhosis. If the illicit liquor traffic could have been controlled, it seems evident that deaths from cirrhosis could have been reduced to a small fraction of 1 per cent. If the death rate were reduced to 0.1 of 1 per cent, this figure would be only 1/50 of the 5 per cent common in recent years. Such a result cannot be accomplished, however, without interfering with the habits of the social and moderate drinkers. Since the majority of the people are social or moderate drinkers, such a program can be enforced only during times of great emergency.

Comment

We believe that this study of 782 cases of cirrhosis concerns the largest series ever considered in a single report. The advantage of large numbers lies in the increased number of patients falling into the different categories making up the study, thus providing better samples.

It now seems to be well established that dietary deficiency secondary to chronic alcoholism is the major etiologic factor in portal cirrhosis in the United States. Wahi[4] has shown that in India dietary deficiency is also the basic factor in this disease. Alcoholism, however, is rare among the Hindus. Dietary deficiency among these people is common due to poorly balanced diets which are largely vegetarian, with deficient protein and often insufficient quantities of food. A number of investigators have demonstrated that enlarged fatty livers with intralobular fibrosis are readily produced in rats by feeding low protein

and low choline-containing diets. Many[13,17,27] have believed that, in experimental dietary-deficiency cirrhosis, fibrosis begins near the center of the lobules about the hepatic veins rather than in the periportal areas.

Alcohol, with its high caloric value, when taken to excess, furnishes considerable energy and tends to depress the appetite for food. An alcoholic person commonly obtains 2,000 to 4,000 calories per day from his whisky alone. Since alcohol furnishes no amino acids for tissue building, while excess calories are present with insufficient lipotropic substance, the liver suffers and fatty metamorphosis frequently ensues. If, at this stage, the patient stops drinking and obtains a good diet rich in proteins and vitamins, recovery is usually prompt. If, on the other hand, drinking continues without treatment, fatty metamorphosis stimulates fibrous tissue replacement of hepatic parenchyma.[10,11] What effects alcohol may have on the liver directly are not known.

The classification of portal cirrhosis into the three phases of subacute, subchronic, and chronic atrophic is one of convenience. The term subacute cirrhosis was first used by Hall and Ophüls[1] in 1925. This has been adopted to some degree and is in common use in California. Subchronic cirrhosis is used in this study to bridge the wide gap often present between a huge subacute fatty cirrhotic liver and the atrophic hobnail liver. Inclusion of the subchronic phase proved to be helpful in the presentation of the statistical data and made possible the use of graphs to advantage. While no sharp differentiation is possible between the subacute and subchronic stages, there is frequently so much fibrosis present in the latter, with the liver still hypertrophied and fatty, that introduction of another stage seemed justified. The differentiation between subchronic and chronic atrophic is usually well defined.

Clinical experience has engendered the concepts that patients with alcoholic cirrhosis suffer to a lesser degree from coronary arterial disease and high blood pressure than do non-cirrhotic patients. The results of this study furnish fairly solid confirmation of the above concepts. Since these ideas are extremely difficult of proof, it would seem that the data here presented are of some importance.

This study again strongly emphasizes the problem of alcoholism in this country. Approximately 80 to 90 per cent of the patients studied were alcoholic so that their disease is chargeable in a high percentage of instances to alcoholism and its first cousin, dietary deficiency. The victims of cirrhosis not only die 10 to 25 years before their time but often are incapacitated for the orderly pursuits of life for years before death. When we consider that death from Laennec's cirrhosis has in

30 years increased from 2 to 5 per cent in one of our large general hospitals, with the figure remaining around the latter percentage for the past 7 to 8 years, it is clear that this problem should be attacked at its source as vigorously as the infectious and degenerative diseases are being attacked.

Summary and Conclusions

This report is a clinical and pathologic study of 782 cases in the Los Angeles County Hospital diagnosed after necropsy as portal (Laennec's) cirrhosis. The period covered was from 1933 to 1946.

Ages ranged from 10 to 90 years. Almost half (49 per cent) occurred between 40 and 60 years. Only 17 per cent died before 40 years while 34 per cent died after 60 years.

Males outnumbered females by 2.2 to 1.

Caucasians (not including Mexicans) numbered 74 per cent, Mexicans 20 per cent, Negroes 4 per cent, and others 2 per cent.

Data on diet was fragmentary. A separate study was undertaken by one of us (A. Y. O.) to determine the nature of the diet, kinds and quantities of alcoholic beverages consumed by cirrhotic patients. Protein was deficient in 45 per cent and B complex in 60 per cent.

Our study revealed that 79 per cent of the patients could be classed as heavy drinkers. Olsen, by personal interview of cirrhotic patients, had found that 92 per cent were heavy drinkers.

The major clinical signs in the patients studied were ascites, edema, jaundice, hepatomegaly, splenomegaly, telangiectasis, hematemesis, dermatitis, and disorientation. The importance of thinking of cirrhosis and alcoholism is emphasized in patients with mild gastro-intestinal complaints, otherwise early cases of cirrhosis may go untreated at a time when reversal of liver changes is possible. (For summary of laboratory data see Table II.)

For convenience, three phases of cirrhosis were recognized: the early fatty subacute with large liver, the intermediate subchronic phase with moderate to marked fibrosis and moderate increase in size, and the chronic atrophic hobnail phase.

Fibrosis of the periportal areas ranged from minimal to moderate in the subacute group; in the subchronic, from moderate to advanced; and in the atrophic group, from advanced to far advanced, the majority falling in the latter group.

There was no definite pattern in the distribution of new bile ducts in the periportal fibrous tissue among the three phases. This was true also of round cell infiltration of the fibrous portal areas.

Fatty infiltration was most conspicuous in the subacute group, only

12 per cent being free of fat. In the subchronic group, 50 per cent contained fat while 23.57 per cent contained fat only to a 1 plus degree. Of the atrophic group 60 per cent contained visible fat and 30 per cent had 1 plus or less.

We believe that in the human subject, as has been shown in experimental cirrhosis due to dietary deficiency, fatty infiltration and enlargement of the liver precede the development of true cirrhosis.

Hepatic necrosis was found in all three phases of cirrhosis but was most common in the subacute. Most of the patients who showed necrosis of the liver had jaundice of some degree.

In 60 per cent of the patients with subacute cirrhosis, the spleen was enlarged. In the subchronic and atrophic phases of the disease, 70 to 75 per cent showed splenomegaly. In 50 per cent of the latter the weights ranged from 200 to 400 gm.

Fatal hemorrhage from esophageal varices occurred in 10 per cent of the subacute group and 25 per cent of the subchronic patients. The incidence was slightly lower (21.6 per cent) in the atrophic group.

Up to 55 years of age *moderate* to *severe* coronary arteriosclerosis was only about 50 per cent as common in the cirrhotic group as in a group of non-cirrhotic controls. The differences after 65 to 70 years were much less marked in the two groups.

The difference in incidence of hypertension in our 782 cirrhotic patients versus a very large group of non-cirrhotic controls was more definitely in favor of the cirrhotic group than was true for coronary sclerosis. Statistical analysis of the incidence of hypertension in 524 male and 249 female cirrhotic patients versus 190 male and 305 female non-cirrhotic controls showed, at age 50, both systolic and diastolic pressures significantly higher in non-cirrhotic than in cirrhotic patients, including both sexes.

Causes of death in cirrhosis fell mainly into four categories: (1) acute and chronic infections which accounted for 33 per cent; (2) hemorrhage from esophageal varices, 19 per cent; (3) hepatic insufficiency, 17 per cent; and (4) cardiac failure, 14 per cent.

This study again emphasizes the seriousness of the problem of alcoholism in this country.

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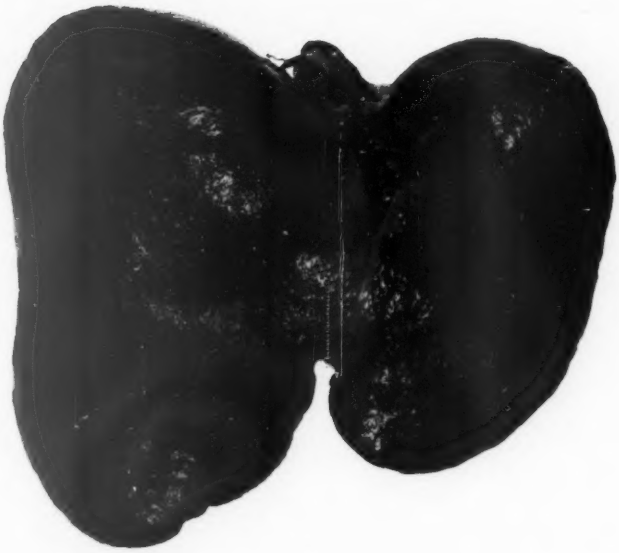
LEGENDS FOR FIGURES

FIG. 1. White female, 46 years old (necropsy no. 46034). Liver in subacute cirrhosis. Large, finely granular, fatty liver. Weight, 3,000 gm.

FIG. 2. White female, 51 years of age (necropsy no. 35275). Photomicrograph of liver in subacute cirrhosis. Heavy drinker for 10 years. There is early fibrosis with hydropic degeneration and necrosis of liver cells. Some hepatic cells show alcoholic hyalin. Fatty infiltration is marked in other areas (3 plus). Liver weight, 3,340 gm. × 285.



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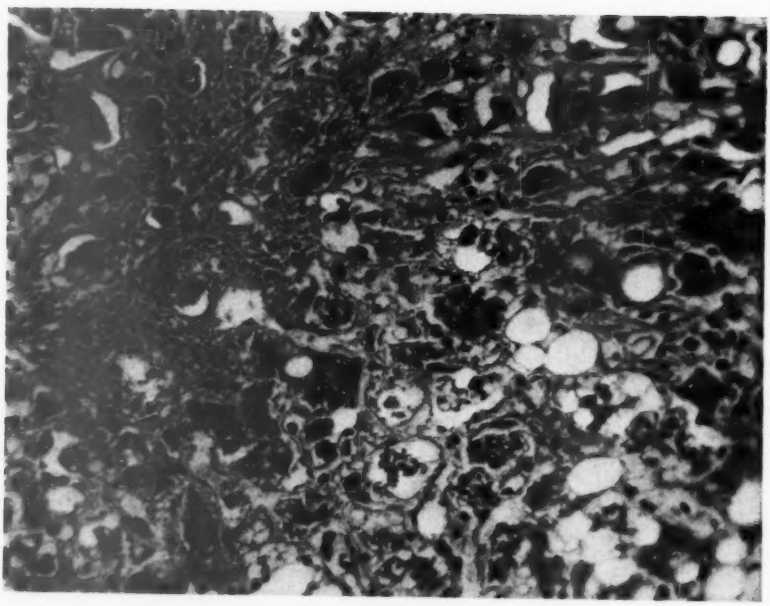

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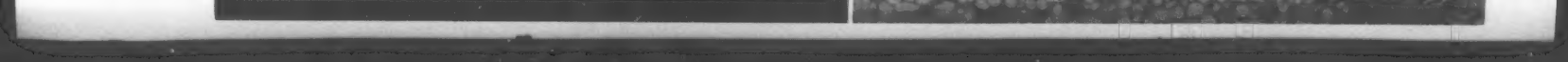
FIG. 3. White male, 58 years old (necropsy no. 28308). Liver in subchronic phase of portal cirrhosis. Large, coarsely granular, fatty liver with marked fibrosis. Weight, 2,000 gm.

FIG. 4. White male, 53 years old (necropsy no. 35244). Photomicrograph of the liver in subchronic phase of cirrhosis. Fibrosis, 3 plus; fatty infiltration, 4 plus; necrosis, 2 plus; hyperplasia (regeneration), 2 plus. Liver weight, 2,980 gm. × 114.



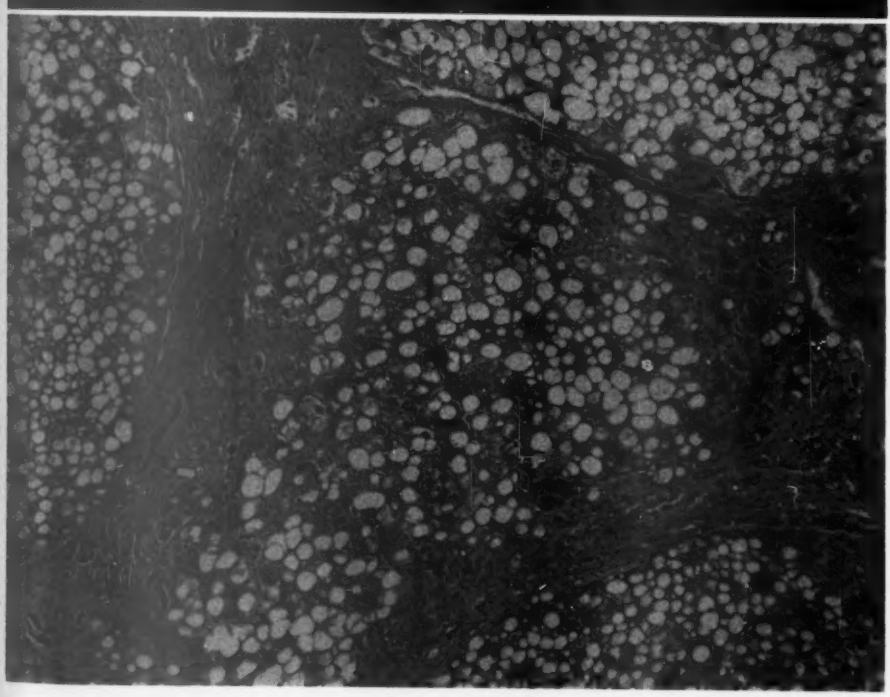
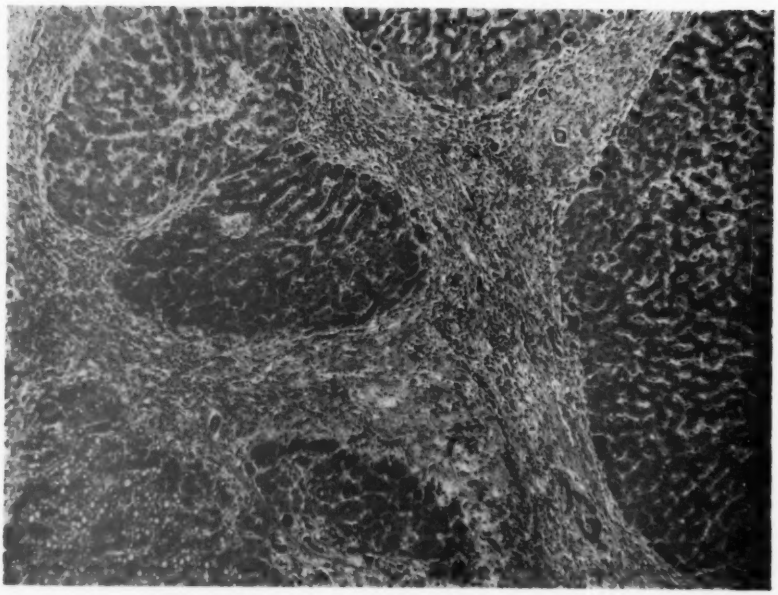


FIG. 5. White female, 64 years old (necropsy no. 46125). Liver in chronic atrophic phase of cirrhosis. Small, hobnail liver with extensive fibrosis. Weight, 1,175 gm.

FIG. 6. White male, 45 years of age (necropsy no. 35404). Photomicrograph of liver in chronic atrophic cirrhosis. No record of alcoholism. Of note are abundant dense fibrous tissue (4 plus), fat (1 plus), necrosis (0), and hyperplasia (4 plus). Liver weight, 980 gm. × 65.

5



6

MYELONECROSIS, EXTRAMEDULLARY MYELOPOIESIS, AND LEUKO-ERYTHROBLASTOSIS

A Mesenchymal Reaction To Injury *

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The purpose of this paper is to describe the histogenesis and morphology of the anatomical lesions of the benign myeloproliferative syndromes. Four such cases which were seen in the surgical pathology and necropsy services of the Department of Pathology at the M. D. Anderson Hospital prompted this study and form the basis of the report.

Hematologists have long recognized a disorder of hemopoiesis characterized by moderately severe normocytic or macrocytic anemia, the presence of immature erythrocytes and granulocytes together in the peripheral blood, and enlargement first of the spleen and then of the liver as a result of myeloid metaplasia.[1-13] The total leukocyte count may be elevated, and there may be megakaryocytes in the peripheral blood, with increased platelets and polyglobulia. The associated lesions of the marrow have been described variously as hyperplasia, atrophy, sclerosis, or fibrosis, and have been related to an atypical form of osteogenesis. Although there may be one dominant cell type in the histologic sections and peripheral blood, all cell lineages participate in the histogenesis of the lesions, and in some cases two or more cell types may proliferate in combination, show quantitatively equal development, and appear in equal prominence.

The clinical manifestations of this disease are insidious and varied. They include asthenia, progressive weight loss, hemorrhagic tendencies, peripheral edema, deep bone pain, and, most significantly, symptoms referable to the enlarged spleen and liver. It is usually the latter which call attention to the disease, and there may be ascites, jaundice, or other signs of hepatic insufficiency. Many cases have coexisting active tuberculosis or other chronic inflammatory diseases. The most commonly implicated etiologic agents include toxic chemicals, toxemias of systemic inflammatory diseases, and hepatic and endocrine dysfunctions.[14] In many cases no causative factor can be established.

Wyatt and Sommers[14] have described the primary lesion of this

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disease as necrosis of immature granulocytes, erythrocytes, and other hemopoietic cells of the marrow. They have also described the sequential development of reactive hyperplasia of the surviving cells of the marrow, atrophy, sclerosis, and finally osteogenesis. There is a similar progression of events in areas of extramedullary myelopoiesis, although it halts with the development of fibrosis. With this logical concept of pathogenesis a number of related but supposedly distinct hematologic syndromes are recognized as varying manifestations of the same disease process at different periods of development and involving different cell lineages. For convenience, I will place these different manifestations in one general category and refer to them as the benign myeloproliferative syndromes.

The multifaceted nature of this lesion complex has led to a confusing nomenclature. The terminology of various investigators has depended upon the tissues involved in their cases, the morphology of the dominant cell types, and whether the lesions were regarded as neoplastic.[10] Since this is a progressive, constantly evolving process of hemopoietic tissue destruction and repair, which is a non-specific reaction to various forms of injury, a term is desirable which describes the primary lesion in the marrow, the secondary tissue reaction in the spleen, lymph nodes, and liver, and the altered hemopoiesis as reflected in the peripheral blood. A generic term applicable to this whole group of diseases is "myelonecrosis, extramedullary myelopoiesis, and leukoerythroblastosis," and it will be used throughout the report. The thesis will be developed that this is a mesenchymal reaction, and, for reasons of consistency, the terminology employed by Maximow will be used in those parts of the report which deal with cytology and histopathology.

Pathologic Anatomy

Gross Anatomical Characteristics

Marrow and Bones. The gross appearance of the marrow depends upon the stage of the disease at the time of examination. Generally, there is uniformity of changes in samples of marrow from different sites, although there may be differences in the intermediate and late stages. In the early period of hyperplasia the marrow is dark red-purple, paste-like, and has little fat. Later it becomes rusty brown, less abundant, and the fat increases as the hyperplastic response is exhausted. The consistency then is stiff and gelatinous, and from this point the changes may proceed with greater rapidity in the marrow cavities of the long bones. Eventually the marrow is quite firm, sclerotic, dirty gray-yellow to white, and there are only scattered islands

of red-brown hemopoietic tissue. These foci of hemopoiesis decrease in size with progression of the disease.

With the advent of severe sclerotic changes in the marrow, the formerly thin cortical bone thickens and the spongy cancellous bone is increased in quantity and consistency. This continues until the marrow cavities are largely replaced by hard, compact bone. In the flat bones the cavities can hardly be identified, and in the long bones only a thin, narrow channel remains. As a rule, death cuts short the progress of osteosclerosis before the development of radiologically demonstrable changes.

Spleen. In the intermediate and late stages the spleen is markedly enlarged and has a tense, dirty blue-gray capsule often covered with adherent fibrous tags. There may be nodular hyaline thickening of the capsule, and the surfaces made by cutting are russet or purple, bulging, and firm. There may be diffusely increased fibrous tissue, and the finger punches through the surface with some difficulty. The normal pattern of trabeculae and follicles is effaced, and the pulp is uniformly meaty in appearance. There may be localized, fairly well circumscribed tumefactions bulging from the cut surfaces. Upon histologic examination these areas prove to be exceptionally active foci of hemopoiesis, and often show masses of megakaryocytes.[2] In the later stages the spleen becomes increasingly rusty brown, a few hemosiderotic nodules may appear, and fibrosis becomes more marked. Infarcts of the spleen are sometimes found in those cases in which polycythemia is a prominent feature.

Lymph Nodes. The lymph nodes are slightly to moderately enlarged in the intermediate stage, and the surfaces made by cutting are soft, bulging, moist, and gray-purple. Later they tend to be smaller, and have firm, flattened, red-brown, fibrotic cut surfaces.

Liver. The liver enlarges during the intermediate stage, but seldom reaches a size comparable to that of the spleen. The capsule is deep red-brown to purple, and generally smooth, although there may be adherent fibrous tags over the surfaces and flecks of fibrin if ascites was present. The edges are rounded, although the general configuration is normal. The surfaces made by cutting bulge slightly, are red-brown, and relatively firm. The cut surfaces may be fatty, gray-yellow, and greasy, with myriads of tiny, punctate, red areas of hemopoiesis. In some cases the cut surfaces may be finely granular and show diffuse fibrosis with nodular regeneration.

Other Tissues. There may be masses of glistening, fibrotic, mottled gray-orange, secondary hemopoietic tissue in the omentum, those seg-

ments of the gastro-intestinal tract bearing lymphoid tissue, and the perirenal and retroperitoneal fat.

Microscopic Characteristics

Marrow and Bones. In the early and intermediate stages of the disease there is marked hyperplasia of all hemopoietic cells, and a tendency toward massing and grouping of each series, although there is some overlapping of cell groups. In those early cases with a polycythemic component, the erythrocytic series predominates, but generally the erythrocytic and granulocytic series are quantitatively equal. There are many hemocytoblasts, and often there are large numbers of megakaryoblasts and megakaryocytes grouped together in syncytium-like structures. The reticular cells representing the fixed undifferentiated mesenchymal cells are prominent, and appear to be increased in number. In the early stages there is a fairly wide range of maturation of cells in the different series, and there may be one or two cell types which are more numerous than others. The cells which are most prominent are largely responsible for the hematologic expression of the different cases. The common denominator of all benign myeloproliferative diseases is the widespread occurrence of foci of necrosis of immature hemopoietic cells. There may be frank cell destruction with local loss of the normal histologic pattern, but generally there are only pyknosis of the nuclei, altered staining characteristics, shrinkage of the cytoplasm, and accumulation of anuclear cell fragments and débris. The process of repair is begun with a hyperplastic response of the primitive hemopoietic cells which in turn undergo focal necrosis. Each succeeding generation of hemopoietic cells is less well differentiated, and eventually the responding cells are hemocytoblasts for the most part.

In spite of sometimes very marked hyperplasia, the over-all reticular pattern of normal marrow obtains, and there is no destruction of bone or other evidence of neoplastic invasion. In the later stages atrophy of the marrow occurs after the hyperplastic response is exhausted. There is progressive atrophy of the hemopoietic cell masses, with persistence of small foci of hemocytoblasts, erythroblasts, promyelocytes, and megakaryoblasts. The fat content increases, and the reticular cells become less prominent. There is simultaneous proliferation of the fibroblastic framework and its vascular component. In the interstices of this net is an oxyphilic, finely granular or vacuolated ground substance termed myelofibrin, which gradually condenses, sometimes becomes laminated, and goes on to fibrosis. Dispersed in

the myelofibrin are free histiocytes containing small granules of hemosiderin. The vascular spaces become larger, and in the loose tissues around their periphery are islands of hemopoietic cells which remain until hemopoiesis has finally ceased.

Terminally there is an atypical form of osteogenesis[8] with calcification of the fibrous ground substance in areas adjacent to bone spicules, osteoid formation, and ossification. Osteoblasts are rare, and osteoclasts are even more unusual. The newly formed bone has a laminated mosaic appearance reminiscent of, but different from, that of Paget's disease. The osteocytes are large, atypical, and in the great majority of instances are formed from fibroblasts rather than osteoblasts.

Spleen. Early in the disease the normal histologic structure of the spleen is obliterated by masses of proliferating hemocytoblasts, immature granulocytes, erythrocytes, plasmacytes, and megakaryocytes. Hemopoiesis takes place from the reticular cells without the sinusoids as well as from the littoral cells of the sinusoids. Cells formed in the extrasinusoidal areas migrate into the lumina of the sinusoids, where they join hemocytoblasts which have budded off from the fixed histiocytes lining the spaces. Here they continue to differentiate, and soon the sinusoids are stuffed with clumps of immature hemopoietic cells of all varieties. In the spleen the sequence of events first observed in the marrow is repeated, starting with a wide range of cellular differentiation, focal necrosis, hyperplasia, reversion to more immature cells, and eventual progression to fibrosis of the pulp. There are dense hyaline bands of fibrocytes which are continuous with the trabeculae. With continuing destruction of erythrocytes and liberation of pigment, the free histiocytes and fixed histiocytes not participating in the hemopoietic response become quite prominent and phagocytize large quantities of hemosiderin. The remnants of the lymphoid follicles do not take part in this reaction.

Lymph Nodes. The lymph nodes show essentially the same process as the spleen. There is obliteration of the normal histologic structure and the follicles are frequently absent. The reticular cells and fixed histiocytes are quite prominent and in the later stages contain quantities of hemosiderin. There may be active hemopoiesis in the sinusoids, although as a rule the lymphoid tissues are exhausted by the time the case comes to the attention of the pathologic anatomist. This is not remarkable in view of the fact that the lymph nodes are the first tissues to show an extramedullary response,[15] and thus the reaction runs its course before death. Usually the nodes are fibrosed and there is only minimal hemopoiesis.

Liver. The liver shows extramedullary hemopoiesis, but to a lesser extent than the spleen. The sinusoidal lumina are stuffed with adult erythrocytes and clumps of dark-staining immature blood cells, particularly in the centrolobular areas. There may be many megakaryocytes. In most cases the liver participates in the blood-forming reaction only to the extent that it filters out hemocytoblasts formed in the spleen and lymph nodes.[15] These cells proliferate and differentiate in the stagnant, slow moving sinusoidal blood with its high carbon dioxide content. This environment is well suited for erythrogenesis, and in the earlier stages the erythrocyte is the dominant cell type in the areas of hemopoiesis in the liver. Later, elements of the granulocytic series become increasingly prominent, and the fixed histiocytes lining the sinusoids and the fixed undifferentiated mesenchymal cells distributed in the stroma are stimulated to hemocytoblastic differentiation, with active proliferation of all cell types both within and without the sinusoids. If there is an extensive reaction without the sinusoids, the normal histologic pattern of the liver may be drastically altered.

Frequently there are many widely scattered foci of necrosis with accumulations of leukocytes, extravasation of erythrocytes, distorted necrotic liver cells, and hyaline débris. There may be fibrosis of these areas as well as of the portal areas. Most of the liver cells contain varying quantities of iron pigment depending upon the duration of the disease, and some cases show frank hemosiderosis.

Peripheral Blood. The peripheral blood reflects the progression of the reaction in the marrow, spleen, and liver. The initial blood picture is unknown, as a rule, since medical attention is rarely directed to the disease until the intermediate or late stages. Approximately 10 to 20 per cent of cases of polycythemia develop myeloid hepatosplenomegaly and leuko-erythroblastosis,[16] and several cases terminating with osteosclerosis have been reported.[17] It is probable that polycythemia is one expression of the myeloproliferative response before exhaustion of the primary blood-forming tissues.

In the intermediate stage there are nucleated erythrocytes in all stages of development and in large numbers out of proportion to the degree of anemia. The erythrocytes show anisocytosis, poikilocytosis, polychromatophilia, and basophilic stippling. There are increased numbers of reticulocytes. The differential leukocyte count shows a left shift of varying degree, with hemocytoblasts, numerous promyelocytes, myelocytes, and metamyelocytes, although the total leukocyte count may be normal or even decreased. Conversely, the leukocytes may be

numerically increased, with the development of a frankly leukemoid blood picture. This occurrence of large numbers of immature erythrocytes and granulocytes together in the peripheral blood, with or without anemia, has been termed leuko-erythroblastic anemia, or leuko-erythroblastosis. Frequently immature megakaryocytes are found in the peripheral blood, with increased numbers of platelets, many of which are abnormally large and show heavy central chromatin nets. Sometimes the platelets occur in packets. The presence of large numbers of immature hemopoietic cells in the sinusoids of the spleen, lymph nodes, and liver goes far to explain the peripheral blood picture.

Other Tissues. Foci of lymphoid tissue in the gastro-intestinal tract and lungs mimic the changes in the spleen and lymph nodes. In the lungs and kidneys, an additional finding is the presence of megakaryocytes and masses of smaller cells that have been liberated from the spleen and nodes, and which have been filtered out in the small capillaries of the septa and glomerular tufts.

Sometimes foci of hemopoiesis can be demonstrated in the capilliform sinusoids of the adrenal and pituitary glands. Presumably the same mechanism obtains here as in the liver, where the hemocytoblasts are filtered out in the sinusoidal pools. It is of interest that the fixed histiocyte system forms the lining of the sinusoids in these endocrine glands, and although they possess hemopoietic capabilities, they seldom show such differentiation.

Illustrative Cases

Case 1, MDAH no. 5224, A–51–29

The patient was a 69-year-old carpenter, who was referred to the hospital for treatment of a recurrent tumor of the skin near the outer angle of the left eye. Routine questioning elicited a history of polycythemia. In April, 1946, it was found that he had an enlarged spleen, with an erythrocyte count of 6.62 millions and a hemoglobin level of 108 per cent. At that time the total leukocyte count was 35,000, with 84 per cent polymorphonuclear leukocytes, 24 per cent of which were immature forms. During the succeeding 5 years the polycythemic blood picture persisted despite repeated phlebotomies. He developed a severe bleeding tendency, and had intermittent episodes of peripheral edema.

The patient was a chronically ill old man with marked peripheral edema. There was a small punched-out, circular, ulcerated tumor of the skin near the outer angle of the left eye, and an adjacent area of irradiation dermatitis. The thoracic skeleton was kyphotic, and the heart was enlarged. There was a harsh systolic murmur over the whole precordium. The lungs were hyperresonant except at the bases, where there was dullness and evidence of pleural effusion. The spleen was hard, movable, and enlarged to a level immediately above the iliac crest. The liver could not be palpated, but was percussed to a level 2 cm. below the costal margin.

The patient was admitted for biopsy and treatment of the skin lesions, and for hematologic investigation. After exhaustive peripheral blood studies and bone mar-

TABLE I
Hematologic Data

Case no.	Total erythrocytes	Hemoglobin	Reticulocytes	Nucleated erythrocytes	Total leukocytes	Hemocytoblasts	Promyelocytes	Myelocytes	Metamyelocytes	Adult neutrophil granulocytes	Eosinophilic granulocytes	Basophil granulocytes	Megakaryoblasts	Megakaryocytes	Monocytes	Lymphocytes	Platelets
1. Admission, 4/25/50	5.00	9.5		2	32,650		3	1	12	64	5	7				8	234,000
Terminal, 11/14/50	3.08	8.6			21,950	1	1	1	4	63	5	10				15	
2. Admission, early 1944	5.78	21.4	2.9		13,300			1	9	75	1	6			4	4	1,540,000
Terminal, 5/50	4.64	12.3			48,000			4	13	64		5			2	12	55,000
3. Admission, 11/8/49		9.6		9	18,950	8	4	10	34	33	2	4	1	2		2	
Terminal, 11/11/49	4.03	11.0			21,350	6	9	12	37	24	2	2		2		6	450,000
4. Admission, 4/5/51	1.94	7.4	2.9	29	29,950	4	2	5	20	44		1			15	9	24,000
Terminal, 2/21/52	2.50	5.0		1	22,650	3	6	7	28	32					6	18	24,000

row biopsy, the diagnoses of "atypical myelosis" and "polycythemia" were made. His condition steadily deteriorated during the next 5 months, with progressive development of right-sided heart failure, anemia, ascites, and increased peripheral edema. The results of representative hemograms early and late in the period of observation are summarized in Table I. The erythrocytes consistently showed poikilocytosis, anisocytosis, ovalocytosis, and polychromatophilia. The leukocytes were consistently increased in number, and in addition to immature forms, there were many older hypersegmented cells. The patient expired at home early in February, 1951, approximately 6 years after the first diagnosis of polycythemia.

Histopathologic Description of the Sternal Marrow

Fragments of the sternal marrow obtained for biopsy by trephine showed hyperplasia. There were no fat cells, and no alteration in the relationship of the marrow substance to the bone. There were clusters of many large, atypical megakaryoblasts and megakaryocytes with multiple lobulated, folded, hyperchromatic nuclei and homogeneous "ground glass" cytoplasm with processes which appeared to be continuous from one cell to another (Fig. 1). Some had engulfed mature erythrocytes, degenerating granulocytes, and other cell débris. There was marked hyperplasia of all cell lineages, although the erythrocytic elements were in slight predomi-

nance. Hemocytoblasts, myelocytes, and erythroblasts occurred in abundance, and eosinophilic granulocytes in all stages of maturation were quite prominent. The reticular cells showed no abnormality. Some fields showed an occasional small area of fibroblastic proliferation. The littoral cells of the sinusoids were swollen and were budding off hemocytoblasts into the lumina, although most of the hemopoietic activity was without the sinusoids. Occasional fields showed large megakaryocytes and immature blood cells extruding into the sinusoids. Within the lumina were masses of all forms of immature hemopoietic cells, precipitated fibrin, and megakaryocytes. The endothelial cells lining the small arterioles were swollen. There was one small, well circumscribed, necrotic area with complete loss of the histologic pattern seen elsewhere in the section. Here there was a central eosinophilic mass of precipitated protein material, with extravasated adult erythrocytes, a few necrotic polymorphonuclear leukocytes, and a peripheral ring of adult leukocytes showing varying degenerative changes. New bone formation could not be demonstrated in any of the sections.

Gross Anatomical Findings at Necropsy

The marrow from the sternum, ribs, and vertebral bodies was abundant, granular, moist, gray-pink and homogeneous. The trabecular elements were sparse and delicate, and the cortices were thin. The femoral and tibial marrow was gray-pink, and appeared to have a greater fat content than in other sites.

The spleen was bulky and weighed 1,020 gm. The capsule was irregularly thickened, and covered with adherent fibrous tags. The surfaces made by cutting were dry, homogeneous, gray-pink, fleshy, and bulging. The normal pattern of trabeculae and follicles was effaced.

The liver weighed 1,829 gm., and showed evidence of chronic passive congestion. Other significant findings included ascites (2,500 cc.), bilateral pleural effusions, coronary arteriosclerosis, and myocardial fibrosis.

Microscopic Findings

The marrow from the sternum, ribs, and vertebral bodies was very hyperplastic. Most of the cells were hemocytoblasts, erythroblasts, and promyelocytes, but all stages of maturation were seen. A remarkable finding was the presence of dense foci of hyperplasia in which the cells, as a rule, were of the younger stages. These areas were demonstrated by holding the slide against a white background, whereupon they appeared as areas of condensation of the marrow substance. The cells of the megakaryocytic series were prominent, but not as in the

material secured for biopsy. Eosinophilic granulocytes were abundant in all sections. There was hemopoietic activity both within and without the sinusoids, although the littoral cells appeared to be participating in the hemopoietic reaction more than was indicated in the biopsy specimen. The sinusoids were stuffed with clumps of immature blood cells and large atypical megakaryocytes, many of which contained phagocytized débris.

Portions of the tibial and femoral marrow showed marked atrophy and myelosclerosis in contrast to that from other sites. There was a loose, myxoid, reticular stroma, in the interstices of which was myelofibrinous ground substance. Dispersed throughout the loosely knit atrophic marrow were occasional immature blood cells, free histiocytes, and plasmacytes. The reticular cells were prominent, and the free histiocytes contained large quantities of hemosiderin. There were many areas of necrosis, with masses of fibrin and extravasated erythrocytes (Fig. 2). The vascular spaces were dilated and had foci of hemopoiesis in their periphery.

The spleen showed marked fibrosis of the pulp. The sinusoids were fairly wide and contained scattered clumps of immature hemopoietic cells. The littoral cells were swollen and budding off hemocytoblasts. Within the pulp were occasional areas in which the reticular cells were prominent. There was moderate hemopoietic activity within the pulp, although megakaryocytes were infrequent. The capsule was thickened, laminated, and densely hyaline.

The sinusoids of the liver were widely dilated, and the cell cords atrophic. The sinusoids contained myriads of adult erythrocytes, although in the central portions there was some erythropoiesis. The hepatic cells showed increased green-brown bile pigment. An additional microscopic finding of interest was the presence of hemopoiesis in an occasional sinusoid of the adrenal glands.

Case 2, A–51–97

The patient was a dentist, 61 years of age, who had complained of hyperhidrosis, frequent occipital headaches, blurring of vision, a florid complexion not associated with exposure to sunlight, and pain in the legs over a number of years. A routine erythrocyte count as part of a general examination in 1942 showed over 6 million cells, and a subsequent count showed 7.5 million. A diagnosis of polycythemia was made and he was treated with phenylhydrazine and repeated phlebotomies. In 1944 he was referred to a hematologist for re-evaluation and further treatment. The erythrocyte count was then 5.78 million, with 2.9 per cent reticulocytes and 21.4 gm. of hemoglobin. The erythrocytes showed moderate anisocytosis and poikilocytosis, while the leukocytes were qualitatively normal. The sternal marrow was hyperplastic and was morphologically consistent with the clinical syndrome of polycythemia vera.

The lower pole of the spleen was palpable immediately below the costal margin. He was treated with radioactive phosphorus and repeated phlebotomies, following which the spleen was reduced in size and there was general clinical improvement. During the next 4 years his erythrocyte count ranged between 5 and 7 million, the leukocyte count ranged as high as 22,000, and his general condition was unchanged except for increased reddening of the skin and mucous membranes. In 1949 there was the onset of progressive enlargement of both the spleen and liver, and immature erythrocytes and granulocytes appeared in increasing numbers in the peripheral blood. Fragments of sternal marrow showed active proliferation of immature hemopoietic cells of all types, and increased numbers of megakaryocytes, although erythropoiesis was not as prominent as in earlier specimens. Liver obtained for biopsy showed no abnormality, although a portion of spleen showed myeloid metaplasia with numerous cells of the granulocytic and megakaryocytic series. He expired in May, 1951, approximately 9 years after the first diagnosis of polycythemia. The results of peripheral blood studies in the early and late periods of observation are summarized in Table I.

Gross Anatomical Findings at Necropsy

The marrow in all sites was deep red-brown, and increased in quantity. It was friable, and easily scraped from the marrow spaces.

The spleen was enlarged, and weighed 2,000 gm. The margins were rounded, and there was a prominent notch on the anterior edge. The capsule was mottled, red-purple to gray-white, and covered with adherent fibrous tags and fibrin deposits. The surfaces made by cutting were bulging, uniformly deep red-purple, and friable. Large quantities of soft pulp could be scraped away on the knife edge. The normal gross structural pattern was completely effaced.

The liver extended from the level of the right fourth intercostal space to the level of the right anterior superior iliac spine. It weighed 6,000 gm. The capsule was red-purple, and the anterior surface was covered by adherent dense fibrous tags. The surfaces made by cutting bulged markedly, were blue-brown, and uniformly firm. Additional significant gross anatomical findings included lobar pneumonia of the lower right lobe, bilateral pleural effusion, and marked congestion and edema of all lobes of the lungs.

Microscopic Findings

The sternal and vertebral marrow showed large numbers of hemocytoblasts massed in dense clusters both within and without the sinusoids, and differentiating mostly toward the granulocytic series. The hemocytoblasts had large, loosely knit nuclei, prominent nucleoli, and little cytoplasm. Most of these cells appeared to arise from reticular cells, but here and there were large, swollen, sinusoidal lining cells showing mitotic activity and budding into the lumina. There, hemopoiesis could be traced in all stages from hemocytoblasts through late

differentiated cells of the granulocytic series. There were a few dense foci of erythropoiesis, particularly within the smaller sinusoids. Many large atypical megakaryoblasts and megakaryocytes were found within and without the sinusoids. Most of these cells had large, lobulated, folded, reticular nuclei with several hyperchromatic nucleoli, and contained phagocytized erythrocytes, leukocytes, and cell débris. Many showed bizarre mitotic figures. Others had foamy cytoplasm, and it was very difficult to distinguish between these cells and the fixed histiocytes of the stroma, which also contained engulfed particles of pigment and sometimes had foamy cytoplasm. The reticular cells were quite prominent and characterized by large, sometimes multiple, vesicular nuclei and stellate cytoplasmic processes forming a stromal framework. There were many areas of focal necrosis with total loss of the normal histologic pattern and replacement by irregular accumulations of fibrinoid material, extravasated erythrocytes, necrotic cell remnants, and protein débris (Fig. 3). Sometimes these areas were frankly hemorrhagic, and around the periphery were grouped large numbers of adult polymorphonuclear leukocytes in varying stages of degeneration. Another frequent finding in the general vicinity of the necrotic areas were large masses of megakaryocytes arranged in a manner suggestive of a syncytium. There were a few patches of fibrosis adjacent to areas of necrosis.

Marrow from a femur showed widespread myelonecrosis and myelofibrosis (Figs. 4 and 5). The large, thin-walled vessels and sinusoids had somewhat flattened littoral cells, with clumps of immature hemopoietic cells in the lumina. In the peripheral areas were foci of hemopoiesis, and occasional large multinucleate giant cells. There were few foci of necrosis, but the most striking feature was the presence of large expanses of myxomatous tissue. There was no new bone formation.

The spleen showed widespread myelopoiesis. The sinusoids were stuffed with clumps of immature cells ranging from hemocytoblasts through well differentiated metamyelocytes and normoblasts. The littoral cells of the sinusoids were large, and sometimes showed mitotic figures and budding into the lumina. The dense extrasinusoidal masses of hemopoietic cells sometimes formed sheets. There were bands of fibroblasts continuous with the trabeculae, and foci of fibrinoid necrosis similar to those in the marrow. The capsule was thickened, laminated, and hyalinized.

The lymph nodes showed replacement of the normal nodal structure by masses and sheets of hemocytoblasts and early differentiating

erythrocytes and granulocytes (Fig. 6). Most of the hemopoietic activity was in the extrasinusoidal areas. Occasional sinusoids contained hemopoietic cells, megakaryocytes, and free histiocytes. The reticular cells were large, prominent, and sometimes contained granules of hemosiderin. Some fields showed fibroblastic proliferation and obliteration of the pulp.

The sinusoids of the liver were packed with clumps of erythrocytes and lesser numbers of granulocytes, many free hemocytoblasts, and moderate numbers of megakaryocytes. The hemopoietic cell masses were in the centrolobular areas, but there were scattered immature cells in the peripheral portions of the lobules. The fixed histiocytes showed little hemocytoblastic differentiation. The liver cell cords were thin and atrophic, and there was some disorganization in the central portions. There the liver cells were pale, showed loss of nuclear detail, and were in some fields frankly necrotic. There were some central lobular cells that showed increased amounts of finely dispersed green-brown bile pigment. Fairly well circumscribed areas of necrosis similar to those in the sternal marrow were encountered. These consisted of central loss of organized structure, with replacement by masses of fibrin, precipitated protein débris, and anuclear cell fragments. In the peripheral areas were masses of degenerating polymorphonuclear leukocytes. The periportal areas were not involved in the hemopoietic reaction, and showed no significant alteration in structure.

The lungs showed bronchopneumonia. Sections taken elsewhere showed a few scattered areas of hemopoiesis in the thickened septal walls, and many large megakaryocytes entrapped in the septal capillaries. The kidneys showed small punctate foci of hemopoiesis in the corticomedullary junction, and many megakaryocytes lodged as emboli in the capillaries of the glomerular tufts. The large, dilated sinusoids of the adrenal glands contained clumps of immature hemopoietic cells, although the fixed histiocytes lining the sinusoids were not forming hemocytoblasts.

Case 3, MDAH no. 4668, A–49–102

The patient, a 49-year-old photographer, complained of weakness and dyspnea. Six weeks before admission he had an acute upper respiratory infection, following which there was a persistent, productive cough. Three weeks before admission he consulted his physician because of exertional dyspnea and fatigue. A diagnosis of chronic myelogenous leukemia was made, and he was treated with one dose of x-irradiation over the spleen. Shortly afterward he noted the onset of abdominal enlargement and peripheral edema. The cervical lymph nodes had been moderately enlarged for a number of years, but they had not changed in size during the present illness.

The patient was an acutely ill man with peripheral edema. The pulse was 120 per minute, and the respirations 36 per minute. There were several freely movable, moderately enlarged, firm lymph nodes in the right posterior cervical triangle and in the pre-auricular areas. There was marked dullness to percussion over both lung bases and diminished breath sounds, suggesting a bilateral pleural effusion. The abdomen was protuberant, and there was ascites. The liver was markedly enlarged, tender, and occupied most of the right side of the abdomen. The spleen was enlarged, tender, and reached a level 3 fingerbreadths below the umbilicus. There was marked pitting edema to the level of the knees. Roentgenograms showed a right pleural effusion with bilateral reticular and patchy infiltration throughout both lungs.

The indirect van den Bergh reaction indicated 0.6 mg. of bilirubin per 100 ml. of blood. The total proteins were 6.3 gm., with an albumin-globulin ratio of 3.3:3. The cephalin flocculation test was negative after 48 hours. The serologic tests for syphilis were negative, and bacteriologic examination of the sputum showed no acid-fast organisms. The hematologic studies are summarized in Table I. Both megakaryoblasts and megakaryocytes were identified in the peripheral blood (Figs. 7 to 9). There were large numbers of atypical platelets with prominent central chromatin nets, and frequently these platelets occurred in packets (Figs. 7 to 9).

The patient was given a digitalis preparation, a mercurial diuretic, antibiotics, and oxygen. The peripheral edema partially regressed, but in spite of this, his clinical condition steadily deteriorated. He developed tetany, abnormal reflexes consistent with an upper motor neuron lesion, and disorientation. He expired on the sixth hospital day.

Gross Anatomical Findings at Necropsy

The marrow was not described by the prosector. The spleen was enlarged and firm, and weighed 1,100 gm. There was a gray plaque measuring 5 by 3 cm. in greatest dimensions and located on the anterior surface. The capsule was mottled, blue-gray, and smooth. The surfaces made by cutting were uniformly red and firm. Very little pulp could be scraped away on the knife edge. There were numerous large, discrete lymph nodes in the periaortic, mesenteric, and femoral areas. These nodes varied from 1 to 3 cm. in diameter. They were firm, and yellow-white when sectioned. The liver was markedly enlarged and weighed 2,800 gm. The capsule was red-brown, smooth, and glistening. The surfaces made by cutting were flat, uniform, friable, and russet colored.

The lungs together weighed 1,300 gm. The pleural spaces were obliterated by dense fibrous adhesions, with the formation of a pleural rind. All lobes were subcrepitant, boggy, and edematous in the posterior portions. The cut surfaces of both lower lobes were uniform, red-purple, and exuded serosanguineous material upon compression. The upper lobes and the right middle lobe were mottled gray-white to dark red-purple, and showed diffuse infiltrations of dense gray-white fibrous tissue. There were numerous enlarged, firm, gray lymph nodes in the paratracheal and anterior mediastinal spaces. Other significant ana-

tomical findings included ascites (1,500 cc.), and edema of the subcutaneous tissue of the feet and legs.

Microscopic Findings

The sternal and vertebral marrow showed similar changes. Myelofibrosis was a prominent feature of samples from both sites, and the hemopoietic activity was not as marked as in the first and second cases (Fig. 10). There were many atypical megakaryoblasts and megakaryocytes in every field. Most of these cells had multiple, lobulated, folded hyperchromatic nuclei of bizarre configuration. Mitotic figures were frequent, and in many places the meshing cytoplasmic processes formed a syncytium-like structure. Atypical platelet formation was seen in all sections. The sinusoids and venous channels were widely dilated, and had enlarged littoral cells with characteristic budding of hemocytoblasts. The lumina contained large aggregations of platelets intermixed with hemocytoblasts, large numbers of megakarycytes, myelocytes, and few nucleated erythrocytes. The stroma of the unsclerosed marrow contained islands of granulocytic cells in all stages of differentiation, and occasional foci of erythropoiesis. There were many wide stretches of empty marrow framework containing only deeply staining myelofibrin, with rare megakaryocytes, occasional free histiocytes, and foci of fibroblastic proliferation. The reticular cells were prominent, and had hemosiderin granules within their cytoplasm. One field showed minimal new bone formation.

The spleen showed large numbers of megakaryoblasts and megakaryocytes with atypical nuclei and frequent mitotic figures as in the marrow. The normal histologic pattern was obliterated and replaced by masses of immature blood cells mostly of the hemocytoblastic and early granulocytic stages (Fig. 11). The sinusoids were dilated and contained masses of immature cells, while the littoral cells showed marked proliferation and differentiation. There was some fibrosis of the pulp and one section showed a healed area of tuberculous caseous necrosis and fibrosis. The capsule was thickened, laminated, and hyalinized.

The lymph nodes showed two concurrent processes. The mediastinal and peripancreatic nodes showed extensive tuberculous granulomatous inflammation and caseation with peripheral fibrosis. In addition, there were active foci of hemopoiesis in the stroma, and the sinusoids contained small clumps of hemopoietic cells, histiocytes, and large megakaryocytes. There was a predominance of the granulocytic and megakaryocytic series.

The liver showed extensive alteration of the normal histologic pattern. The centrolobular areas were involved in a marked hemopoietic response, and there were many large megakaryocytes with bizarre, hyperchromatic nuclei often showing mitotic activity (Fig. 12). The central liver cell cords were thin, atrophic, poorly stained, and in some lobules necrotic. In the necrotic areas there was total replacement by sheets and masses of granulocytes, erythrocytes, and megakaryocytes in early stages of differentiation. The hepatic cells contained variable amounts of green-brown bile pigment. The portal areas were moderately fibrotic and contained a few hemopoietic cells. The fixed histiocytes were actively differentiating toward hemocytoblasts; occasional focal areas of fibrinoid necrosis were encountered apart from the areas of pressure atrophy.

The kidneys showed small foci of hemopoiesis in the venous channels and many glomerular tufts contained embolic megakaryocytes.

Case 4, MDAH no. 6544

A retired Negro farmer, 68 years old, complained of vague epigastric discomfort, postprandial nausea, and weight loss of 25 lbs. over a 3-year period. The patient was emaciated and chronically ill. There was an irregular, hard, non-tender, mobile mass occupying the left upper quadrant and descending into the epigastrium. The liver was not palpable. There were several moderately enlarged axillary lymph nodes.

The erythrocyte count was 3.87 million, with 6.8 gm. of hemoglobin. The total leukocyte count was 24,300, with one basophilic granulocyte, 2 myelocytes, 18 metamyelocytes, and 50 adult neutrophilic granulocytes in 100 white cells. A presumptive diagnosis of leukemia was made. Repeated attempts at marrow aspiration from several sites failed to yield any material. Tissue was taken for biopsy of the left sixth rib, and excision of an axillary lymph node was done, following which he was discharged to the out-patient clinics. He was treated with repeated transfusions and supportive therapy. After 3 months he complained of severe chronic pain in the region of the right first metatarso-phalangeal joint. A roentgenogram showed gouty arthritis, and a blood uric acid determination was reported as 18 mg. per 100 ml. of blood. Otherwise his clinical condition remained unchanged. Tabulated hematologic findings are summarized in Table I. The numerous nucleated erythrocytes and anemia were prominent features throughout the time he was seen in the clinics. He died unattended at home on April 11, 1952, approximately 13 months after the first admission to the hospital. Necropsy was not done.

Histopathologic Description of an Axillary Lymph Node and Marrow Taken from the Left Sixth Rib

Sections of the lymph node showed slight hyperplasia of the fixed histiocytes and the reticular cells. There were a few areas of hemopoiesis in the peripheral sinusoids, and in the fibrous tissues of the capsule. Only occasional megakaryocytes were encountered.

The costal marrow showed a loose, myxoid stroma of reticular cells

and myelofibrinous ground substance without any appreciable hemopoietic activity. There were a few scattered plasmacytes, histiocytes, and young blood cells. The reticular cells and free histiocytes contained phagocytized hemosiderin granules. There were many fat cells, but no new bone formation (Fig. 13).

COMMENT ON THE CASES PRESENTED

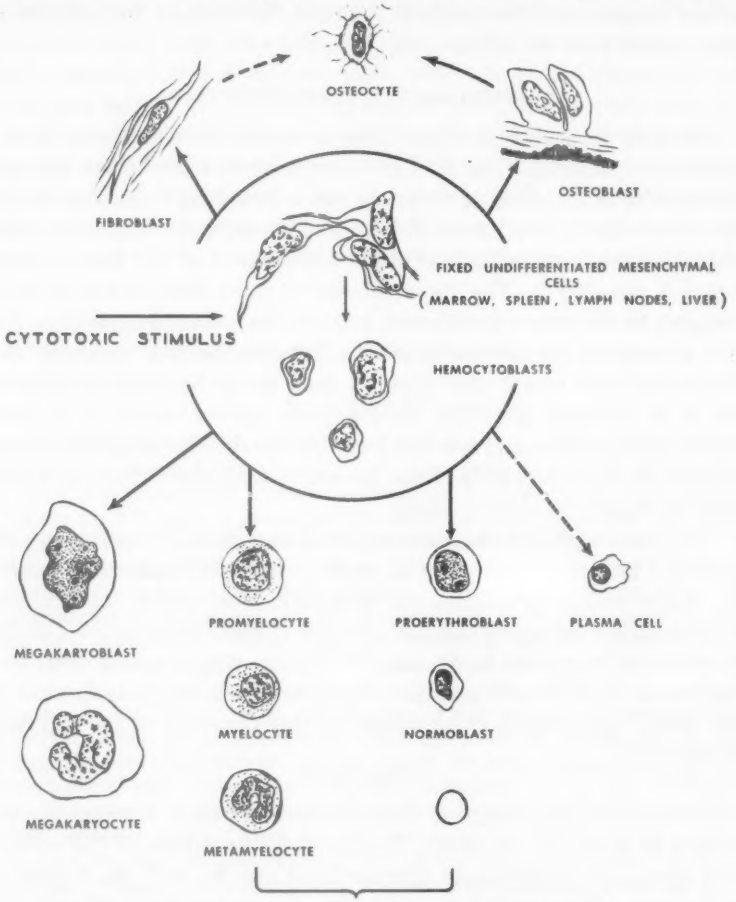
The four cases represent four different manifestations of one underlying tissue reaction. The first and second cases were known to have begun with polycythemia, while the early hematologic findings in the third and fourth cases are not known. The sequence of presentation was arranged to correspond with the development of the disease process as I visualize it. The three necropsied cases showed very similar changes in the marrow, differing only in the extent of atrophy. All had a common myelonecrotic lesion. The only marrow specimen obtained from the fourth case failed to show active hemopoietic centers, but it is probable that the myelonecrotic lesions would have been found if any active marrow had been obtained. The peripheral blood picture of leuko-erythroblastosis or leuko-erythroblastic anemia was seen eventually in all four cases.

The third case is a classic example of the disease that has run its course. There was myelosclerosis, massive myeloid hepatosplenomegaly, severe leuko-erythroblastosis, and co-existing active tuberculosis. A remarkable feature of this case was the predominance of cells of the megakaryocytic series in the marrow, spleen, lymph nodes, liver, and peripheral blood. There were also large numbers of atypical platelets in the blood. This case is quite similar to that reported by Downey and Nordland.[2]

Discussion

The cellular pathology of this disease suggests a non-specific response by a cell type to injury. The lineal differentiation of the various cell types, the predominant differentiated cell(s), and the degree of maturation all determine the histologic characteristics. All cells involved in the continuous process of destruction and repair have common origin from the fixed undifferentiated mesenchymal cell of Maximow, who demonstrated that in the embryo the primitive mesenchymal cells of the connective and hemopoietic tissues form two cell lineages[3,18] (Text-fig. 1). One is the fibroblast, with restricted developmental possibilities, and the other is the undifferentiated mesenchymal cell with almost unrestricted potentialities. These latter are capable of forming histiocytes, hemocytoblasts, fibroblasts, fat cells,

and osteoblasts throughout life.[18-21] They are particularly numerous in the marrow, spleen, lymph nodes, and submucosal fat of the gastro-intestinal tract, where they occur massed in close association with the



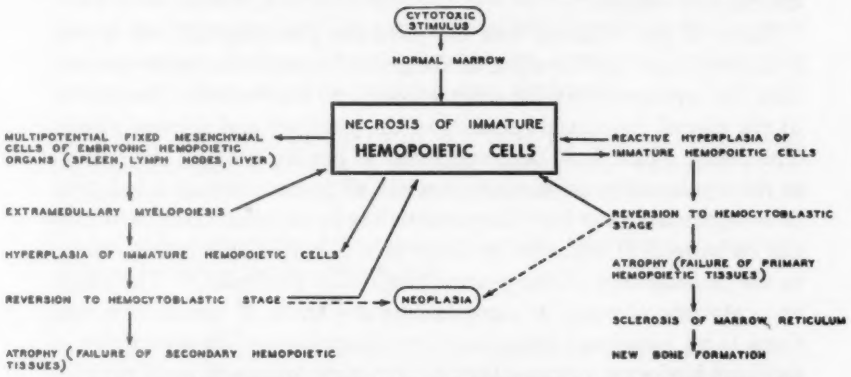
DIAGRAMMATIC REPRESENTATION OF THE CELL TYPES IN THE HISTOGENESIS OF THE LESIONS OF MYELONECROSIS, EXTRAMEDULLARY MYELOPOIESIS AND LEUKOERYTHROBLASTOSIS

Text-fig. 1

reticulin fiber network and are known as reticular cells. As fixed histiocytes (the so-called reticulo-endothelial cells), they form the lining cells of the sinusoids of the spleen, marrow, lymph nodes, liver, and of the pituitary and adrenal glands. As free histiocytes, they occur in fibrous tissue, fat, and serosal membranes throughout the body. Thus there is carried over into the adult organism a large, widely

disseminated, pluripotential cell system which is concentrated in the marrow, spleen, lymph nodes, and liver. Normally these cells remain quiescent, but they retain latent capabilities, and are sensitive to a number of trophic stimuli. The anatomical distribution of this system and its latent potentialities are of the greatest significance in the pathogenesis of the benign myeloproliferative syndromes.

In the early lesions of myelonecrosis the compensatory hyperplastic cells of both the granulocytic and erythrocytic series show relatively advanced maturation. With progression of the disease there is a gradual reversion to less well differentiated cells as the destructive process



Text-fig. 2. Diagrammatic representation of the sequence of events in myelonecrosis, extramedullary myelopoiesis, and leuko-erythroblastosis and the possible relationship to neoplasia.

outstrips the reparative. This continues until the hemocytoblasts largely disappear and the surviving reticular cells become more prominent. Finally the myelofibrin ground substance is laid down, with eventual fibrosis and osteogenesis (Text-fig. 2). It is conceivable that continued exposure of the mesenchymal cell system to a variety of cytotoxic factors could produce this histopathologic evolution.

The nature and mode of action of the cytotoxins can only be postulated. Wyatt and Sommers[14] have suggested that through some abnormality in the respiratory enzyme systems, the liver cells are rendered incapable of completely breaking down organic compounds containing phenol and quinone groups, and conjugating their toxic end products. Such a diverse group of compounds includes chemicals with benzene ring structures and endocrine steroids. In any event, because of this functional defect the hemopoietic cell mass is exposed to high concentrations of cytotoxic materials, with resulting necrosis and liberation of nucleoproteins. There is experimental evidence that nucleo-

proteins have a myelostimulatory action, and can induce both the proliferation of the immature hemopoietic cells of the marrow and the differentiation and proliferation of the undifferentiated mesenchymal cells of the spleen, lymph nodes, and liver. This would also seem to hold true in this disease. The newly formed cells are less well differentiated than the original cells of the blood-forming tissues, and are therefore more sensitive to injury. Thus is the cyclic process initiated in the marrow, and continued in the spleen and liver. Extramedullary myelopoiesis then may be looked on, not as a compensatory reaction, but as an expression of the latent capabilities of the primitive mesenchymal cell system.[20]

There is also evidence that the primitive mesenchymal cell system is an end organ participating in the general adaptation syndrome, and that the myeloproliferative reactions are one expression of derailment of the normal functional relations of the pituitary and adrenal glands. The agents which have been suggested as having etiologic importance in the myeloproliferative syndromes are all potent stressor substances. It is significant that the "karyoclastic" lysis of fixed "lymphoid" tissue by steroids is regarded by Selye as a non-specific reaction related to the development of the general adaptation syndrome.[22] The essential cytologic changes in these lesions are those of necrobiosis, and there is an associated response of proliferation and hyperactivity of the fixed histiocyte system. Possibly the early lesions of myelonecrosis are the analogues of the karyoclastic lesions of the experimental animal. That there is an endocrine control of hemopoiesis has been known for some time, although the mechanism is poorly understood. This idea is supported by the clinical observation that polycythemia is a feature of hypercorticoidism (Cushing's syndrome), and, conversely, pancytopenia is a feature of hypocorticoidism (Addison's disease).

The concept of a general cell response with varying manifestations fits in well with Dameshek's speculations on the myeloproliferative syndrome.[16] He has suggested a possible relationship between myeloid metaplasia, leuko-erythroblastosis, and polycythemia on the one hand, and the leukemias and erythremic myelosis on the other hand. There is often conversion from one of these clinical entities into another of the same group, and it is possible that at some point in the evolution of a benign myeloproliferative disease the immature cell(s) become fixed morphologically, and acquire the inability to respond to the stimuli ordinarily governing their growth and differentiation. Then, instead of going on to exhaustion of the hemopoietic cells, fibrosis, and bone formation, the affected cells would continue elaborating their

own kind at fixed developmental stages. Such a sequence of events would clarify the relations of the benign reactive myeloproliferative syndromes to the malignant neoplastic myeloses, and would explain the conversion from one to another.

Summary

The morphology and histogenesis of the lesions of the benign myeloproliferative syndromes have been described. Four illustrative cases, representing varying stages in the development of the disease, were reported. The myeloproliferative syndromes are considered to be variations of a general mesenchymal reaction to several types of injury. The term "myelonecrosis" is suggested as best describing the primary histopathologic lesion. The etiology of the myeloproliferative syndromes and their inter-relationships were discussed.

I wish to acknowledge my indebtedness and express my thanks to Dr. C. C. Shullenberger, hematologist to the M. D. Anderson Hospital, for his encouragement and assistance in preparation of this manuscript. I wish also to thank Dr. C. Spurr for permission to include the second case in this report, and the members of the Department of Medical Illustration of the Anderson Hospital for the diagrams and assistance in the preparation of the photomicrographs.

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LEGENDS FOR FIGURES

FIG. 1. Case 1. Tissue taken by trephine for biopsy of the sternal marrow. There is marked hyperplasia of all cellular elements, with slight predominance of the erythrocytic series. There is one small area of necrosis, and numerous large megakaryocytes. × 120.

FIG. 2. Case 1 (necropsy). Hyperplasia, focal necrosis, atrophy, and sclerosis of the femoral marrow. Two areas of necrosis are visible. × 120.

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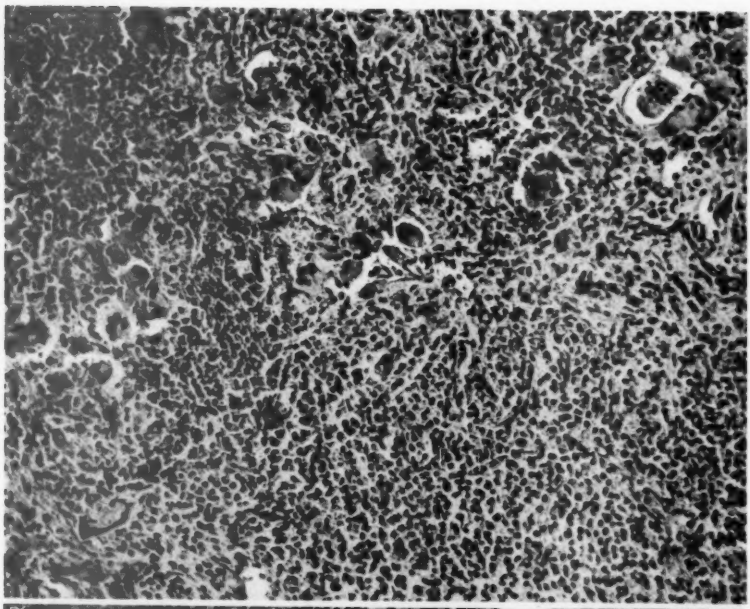

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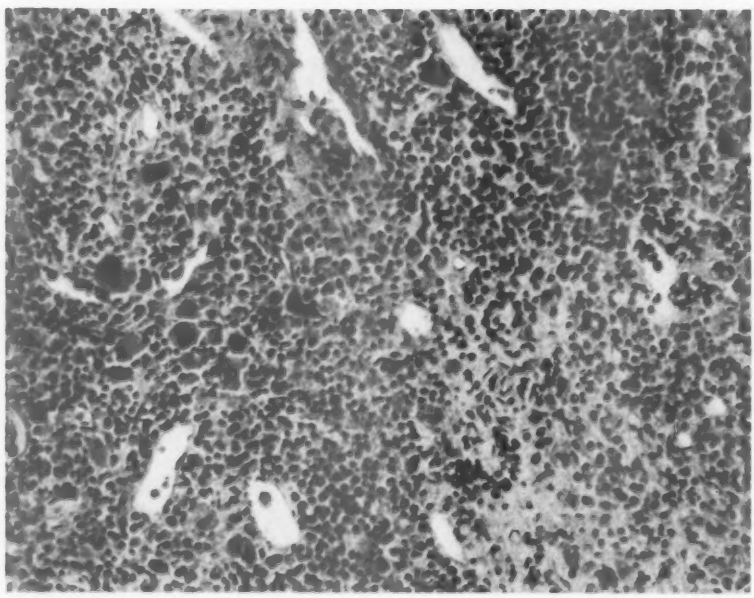
FIG. 3. Case 2 (necropsy). Focal necrosis of the sternal marrow. Hemopoietic activity is moderate. Megakaryocytes are prominent. × 120.

FIG. 4. Case 2 (necropsy). Diffuse atrophy and early sclerosis of the femoral marrow. There is one remaining island of hemopoietic activity. × 35.

FIG. 5. Case 2 (necropsy). Higher power view of a field from the same region as Figure 4. Myelofibrin ground substance fills the interstices of the net of fibroblasts and reticular cells. Hemopoietic activity is at a minimum. × 120.



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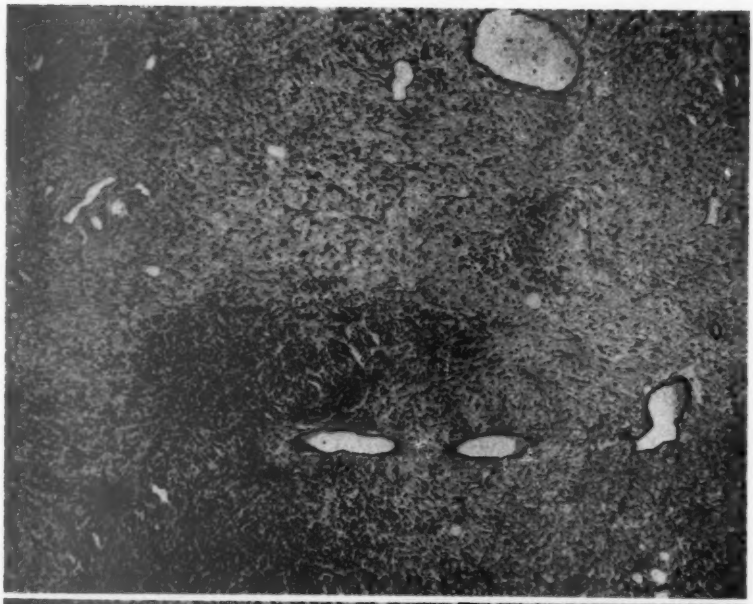

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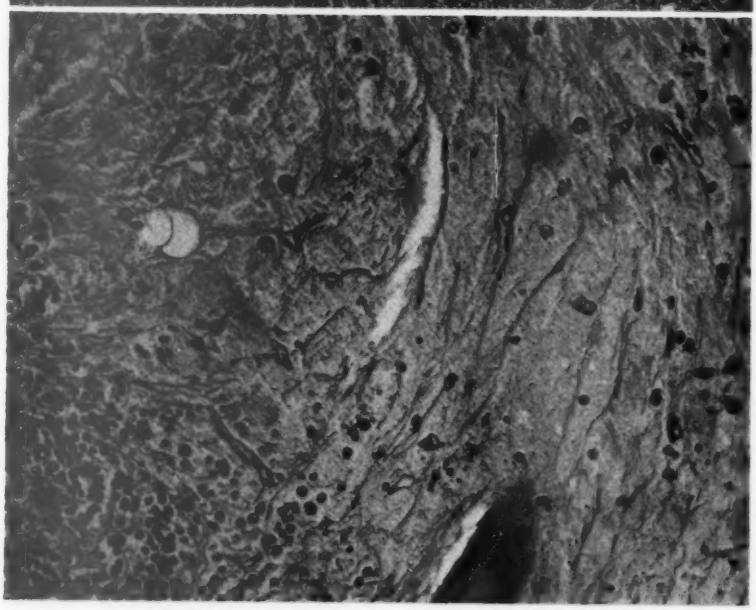
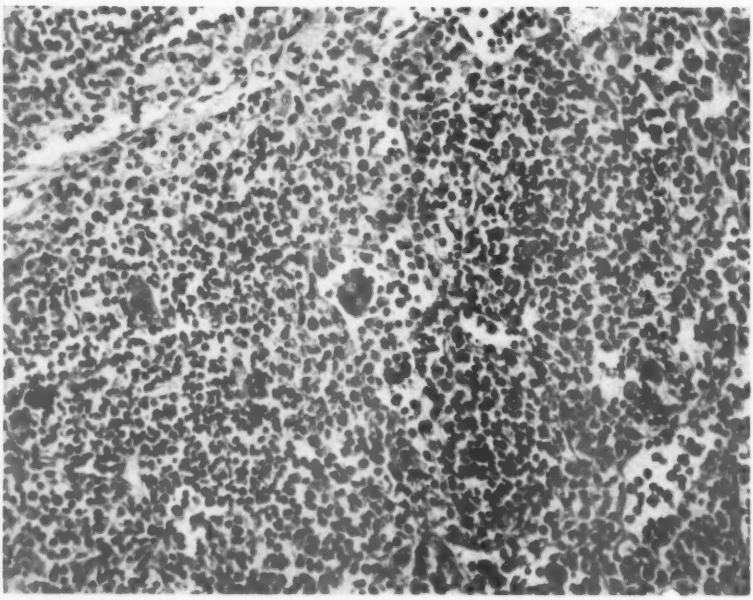


FIG. 6. Case 2 (necropsy). Extramedullary myelopoiesis in a mesenteric lymph node. × 120.

FIGS. 7 to 9. Case 3. *Fig. 7.* Megakaryoblast in the peripheral blood. × 900. *Fig. 8.* Megakaryocyte in the peripheral blood. × 900. *Fig. 9.* Atypical megakaryocyte and abnormal platelets in the peripheral blood. × 900.

FIG. 10. Case 3 (necropsy). Atrophy and sclerosis of the sternal marrow. The megakaryocytes are prominent, and hemopoietic activity is slight. × 120.



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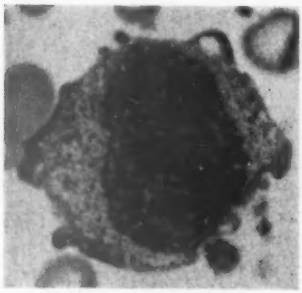

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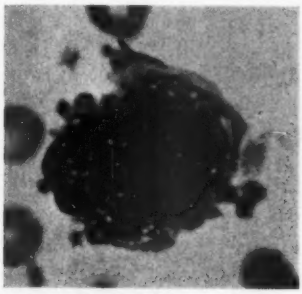

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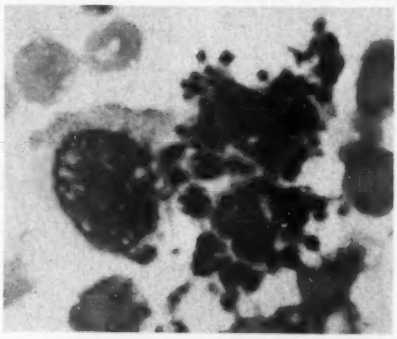

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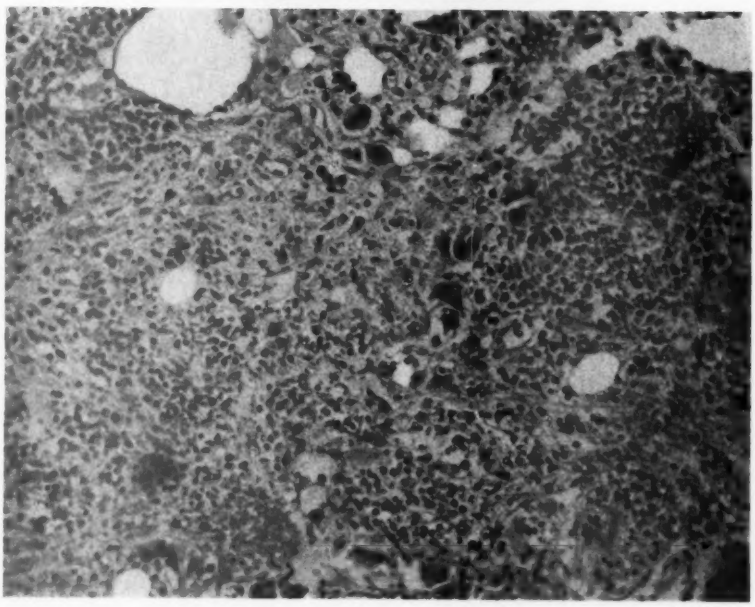
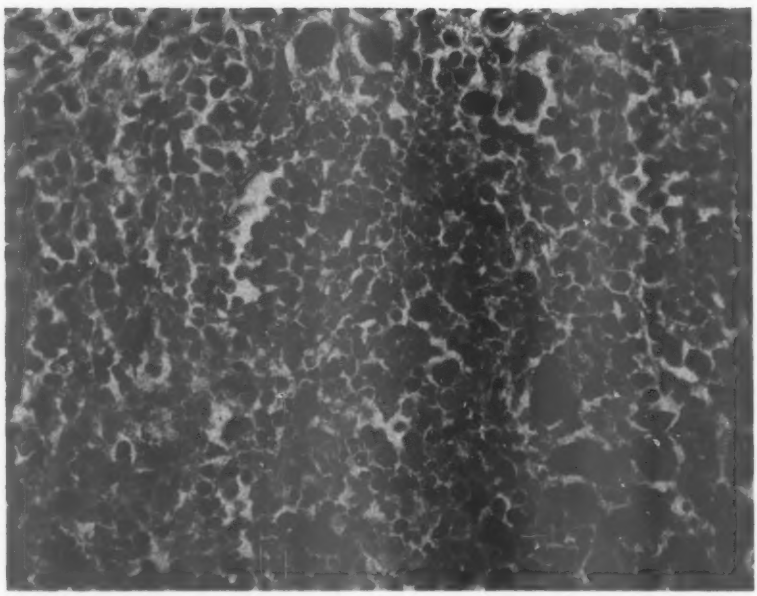


FIG. 11. Case 3 (necropsy). Extramedullary myelopoiesis in the spleen. There is hemopoietic activity both within and without the sinusoids. × 220.

FIG. 12. Case 3 (necropsy). Extramedullary myelopoiesis in the liver. The reaction is largely in the central lobular areas, and there is atrophy and necrosis of the central cord cells. Megakaryocytes are prominent. × 220.

FIG. 13. Case 4. Tissue taken for biopsy from the costal marrow. The marrow is completely replaced by myelofibrin ground substance, and is undergoing sclerosis. There is no hemopoietic activity. × 35.



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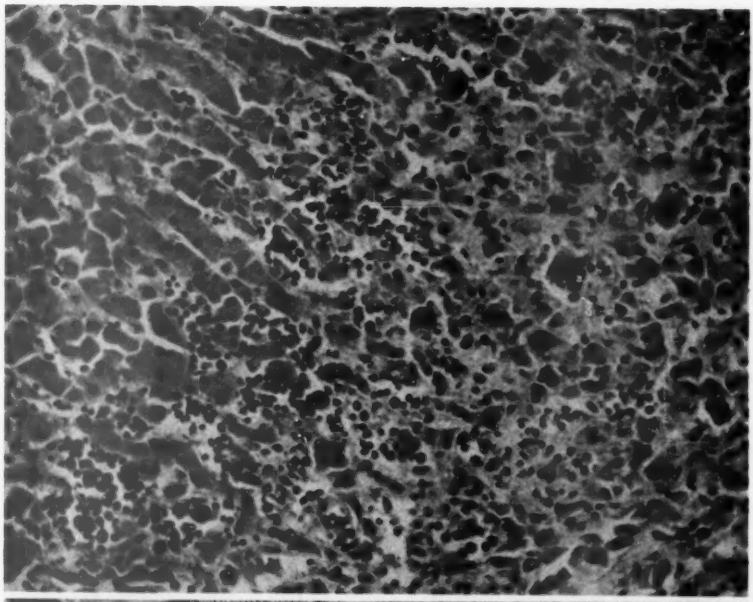

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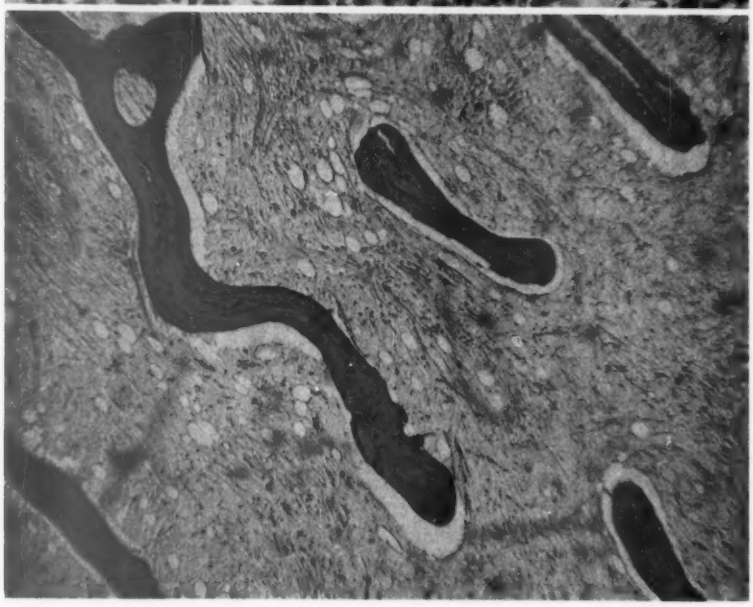

SYSTEMIC NODULAR PANNICULITIS *

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In 1892, Pfeifer[1] described a patient with subcutaneous nodules in the extremities and in the trunk. The nodules were freely movable, red, and were associated with fever. A similar condition was reported by Gilchrist and Ketron[2] in 1916, who noted the ingestion of fat by macrophages as an essential change in the lesion. Weber,[3] in 1925, described the third patient and gave the name of "relapsing, non-suppurative nodular panniculitis" to the disease, which was characterized by the presence of multiple subcutaneous nodules. In 1928, Christian[4] added the fourth case and also the term "febrile" to the name. Brill[8] was the first to refer to the condition as "Weber-Christian disease." Since then some 43 additional cases have been reported (Table I).[5-39]

SUBCUTANEOUS NODULAR PANNICULITIS

The subcutaneous nodules appeared on extremities, abdomen, chest, and back. They varied from 1 to 12 cm. in diameter. They were slightly red and sometimes tender.[25] The nodules either disappeared,[34] to recur frequently, or were reduced in size and fixed by proliferating connective tissue. After disappearance of nodules, there were areas of atrophy with depression of the skin which was adherent to the subcutaneous tissue. Very infrequently, the nodules showed superficial ulceration.[23]

Histologically, the lesion was well defined, limited to the subcutaneous tissue, and showed progressive changes.[34] At first, when the nodules were barely palpable, there were edema, congestion, exudation of polymorphonuclear cells between fat cells,[38] and mononuclear phagocytes with ingested fat.[25] In the second phase, that of the mature lesion, there was an appearance of patchy necrosis of fat tissue.[9,23,25,32] The cell membrane of the fat cells ruptured, the cells collapsed, and were flattened.[23,28] Lymphocytes and phagocytes invaded the fat cells. The phagocytes became distended with ingested fat and lymphocytes. The epidermis and the dermis remained uninvolved.[32] The cellular exudate between fat cells was composed of neutrophilic polymorphonuclear leukocytes, lymphocytes, plasma cells, and macrophages.[9]

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Many of the fat cells and the vacuoles in the macrophages did not take the fat stain.[23] Disintegrated fat cells and free fat droplets were present in the tissue.[9] A rare giant cell could be found.[9] Periarteritis with intimal proliferation,[9,23,32] edema of vessel walls,[23] swelling of elastic fibers, and perifolliculitis characterized the lesion at this stage.

In the third or the atrophic phase,[23] connective tissue had replaced much of the inflammatory activity.[25,34] Giant cells were present in most of the nodules. In some lesions, inflammatory reaction persisted with the lymphocyte as the predominant cell. The vascular changes consisted of periarteritis with organization and intimal proliferation.[9] Scar tissue produced a contraction of the nodule with adhesion of the subcutaneous tissue to the epidermis and depression of the latter.

The clinical manifestations were indefinite. The condition attacked both sexes and all ages. The youngest patient was 23 months old,[24] and one of the older was 64 years of age.[11] The female appeared to be more prone to the disease. Recurrent, slightly tender, subcutaneous nodules, either freely movable or fixed to skin, occurred on arms and legs and less frequently on chest, back, abdomen, feet, and face. Malaise, and general weakness with fever were frequently associated with the first two phases of nodule formation. Fever ranged up to 104° F. Less often there were generalized aching pains, chilly sensations or frank chills, loss of weight,[9] nausea, headaches, joint pains,[5] and enlargement of the liver, spleen, and lymph nodes. The attacks lasted for periods varying from 1 month[21,22] to 15 years.[5,9] Occasionally, anemia was encountered. The number of red blood cells varied from 1.5 to 3.5 millions with the hemoglobin from slightly over 5 to 8.5 gm. The sedimentation rate, when done, was increased slightly to moderately. The white blood cell picture varied from leukopenia of 1,800[23] to marked leukocytosis[2] with an increase in the number of granulocytes. Death occurred seldom. Two of 27 patients died, one of them from intercurrent tuberculosis. Other conditions which may simulate panniculitis are Dercum's disease, erythema nodosum, erythema induratum,[24] subcutaneous sarcoidosis,[11] and post-traumatic fat necrosis.[28]

ETIOLOGY

The cause of nodular panniculitis has not been established. In one compilation of 28 patients, 8 had received either bromides or iodides.[24] In some patients bacterial infection appeared to precede the development of panniculitis.[5,13] As it is true with other conditions of unknown cause, many factors have been implicated. They include:

Injuries of chemical, thermal, and mechanical nature

Drug sensitivity, especially to iodides and bromides
Bacterial allergy
Avitaminosis
Injection of various substances such as insulin and hypertonic dextrose
Infectious diseases, including virus infection

If one or more stimuli such as drugs and infections can produce the lesion of panniculitis, it must be assumed on the basis of the rarity of the condition that unusual susceptibility of the adipose tissue exists in certain predisposed individuals. Very few of the patients had a personal or family history suggestive of allergic manifestations. However, a specific hypersensitivity may be assumed without evidence of the usually accepted evidences of allergy.

NECROPSY REPORTS

There are 6 recorded necropsies on patients with panniculitis.

Miller and Kritzler,[28] in 1943, reported the first necropsy on a 34-year-old woman with multiple recurrent nodules who was ill for 18 months prior to death. Histologic examination of a subcutaneous nodule showed changes consistent with nodular panniculitis. There was splenomegaly (360 gm.), and moderate hepatomegaly (2,440 gm.). The spleen and liver showed areas of focal necrosis, centrolobular in the latter organ, with fatty metamorphosis. The reticulo-endothelial cells of the spleen and the Kupffer cells of the liver were engorged with red blood cells. The lipid of the adrenal cortex was reduced.

The second necropsy was performed by Spain and Foley,[25] in 1944, on a 51-year-old male who was ill for 10 days prior to death. The patient was in an acute alcoholic state and in the end stage of chronic glomerulonephritis. A subcutaneous nodule showed histologic changes consistent with nodular panniculitis. Similar nodules were found in mesenteric, omental, and pretracheal fat.

Friedman[27] reported the third necropsy in 1945. The patient was a 23-year-old white girl who had had recurrent crops of subcutaneous nodules for 5 years and died of staphylococcic bacteremia. There was splenomegaly (350 gm.) and hepatomegaly (2,200 gm.) with many fat droplets in the liver. The spleen contained many phagocytes filled with red blood cells.

The fourth necropsy was presented by Ungar[31] in 1946. The patient was a 37-year-old woman with recurrent subcutaneous nodules, who died of peritonitis. She had nodules in the adipose tissue surrounding the abdominal organs and of the omentum and mesentery.

TABLE I
Reported Cases of Nodular Panniculitis

Authors	Year	No. of cases	Pertinent remarks
Pfeifer[1]	1892	1	
Gilchrist and Ketron[2]	1916	1	
Weber[3]	1925	1	Introduced the present name
Christian[4]	1928	1	Added the term "febrile"
Alderson and Way[5]	1933	1	
Netherton[6]	1933	1	
Weber[7]	1935	1	No biopsy
Brill[8]	1936	1	Introduced "Weber-Christian disease"
Bailey[9]	1937	5	Review
Reed and Anderson[10]	1937	1	
Cummins and Lever[11]	1938	1	
Shaffer[12]	1938	1	
Puente[13]	1938	1	
Binkley[14]	1939	1	
Hartwell, Thannhauser[15]	1940	1	
Tilden *et al.*[16]	1940	2	Summary of 9 previous cases
Hazel and Lamb[17]	1940	2	No tissue examined
Skiöld[18]	1940	1	
Ziegert[19]	1940	1	
Hanson and Fowler[20]	1941	1	
Larson and Ootkin[21]	1941	1	
Rosenberg and Cohen[22]	1942	1	
Miller and Kritzler[23]	1943	1	Review of 26 cases and first reported necropsy, visceral changes without involvement of perivisceral fat
Larkin *et al.*[24]	1944	1	Review of 27 previous cases
Spain and Foley[25]	1944	1	Second necropsy, lesions in mesenteric, omental, and pretracheal fat
Arnold[26]	1945	1	
Friedman[27]	1945	1	Third necropsy, splenohepatomegaly
Ives[28]	1945	1	
Pierini *et al.*[29]	1946	1	
Zee[30]	1946	1	
Ungar[31]	1946	1	Fourth necropsy, widespread panniculitis and intra-abdominal lesions
Mostofi and Engleman[32]	1947	1	Fifth necropsy, perivisceral lesions
Bunnell and Levy[33]	1948	1	
Johnson and Plice[34]	1949	1	Reviewed 35 cases; three stages
Kennedy and Murphy[35]	1949	1	Review
Rubin and Bland[36]	1949	1	
Bendel[37]	1949	1	Review
Brudno[38]	1950	1	
Hanrahan *et al.*[39]	1951	1	Sixth necropsy, splenohepatomegaly
Eisaman and Schneider[40]	1951	1	

The fifth necropsy was performed by Mostofi and Engleman,[32] in 1947, on a 38-year-old man who was ill for 7 months. Subcutaneous nodules appeared 6 months after the onset of illness and presented histologic changes consistent with nodular panniculitis. There was moderate hepatomegaly (2,275 gm.) with extensive fatty changes and focal necrosis in midzonal and central areas. Changes like those of nodular panniculitis were found in the epicardial, peripancreatic, intralobar, perirenal, periadrenal, and mesenteric fat. There was reticuloendothelial hyperplasia of the spleen and lymph nodes with decrease of lymphoid tissue.

Hanrahan, Ippolito, and Dilworth[39] presented the sixth necropsy in 1951. The patient was a 20-year-old woman who was ill for 3 months before death. She had subcutaneous nodules in the extremities and face, with histologic changes of nodular panniculitis. Hepatomegaly (3,400 gm.) and splenomegaly (500 gm.) were found. The liver contained much fat. No other significant changes were found.

Of the 6 reported necropsies on patients with nodular panniculitis, 4 may be distributed into three categories. The necropsies of Friedman[27] and of Hanrahan, Ippolito, and Dilworth,[39] which showed no pertinent abnormal visceral changes except for splenomegaly and hepatomegaly, are excluded. If nodular panniculitis in some way contributed to these two deaths, the subcutaneous lesions may be assumed to be responsible. Since no pertinent visceral changes were identified in these two necropsies, they can be considered to represent a local, subcutaneous phase of nodular panniculitis. The necropsies of Spain and Foley[25] and of Ungar[31] showed nodular lesions of the perivisceral adipose tissue and of the mesentery and omentum. The similarity of the lesions justifies the inclusion of these two patients in the first category of systemic nodular panniculitis. The necropsy of Miller and Kritzler[23] disclosed areas of focal necrosis of the liver and the spleen without perivisceral nodular lesions. This case may be considered as the second type of systemic nodular panniculitis. The necropsy of Mostofi and Engleman[32] revealed both types of visceral lesions, the perivisceral nodules and focal necrosis. The findings in this patient suggest that both types of lesions represent the manifestations of systemic nodular panniculitis and that this case falls into the third category.

REPORT OF CASES

Case 1

The patient was a white woman, 61 years of age, who was followed from April, 1941, to her death in October, 1949. Her first entry to the hospital in April, 1941, was

for right hemiplegia and aphasia. Her red blood count was 3.5 millions; hemoglobin, 6.2 gm.; white blood count from 8,800 to 13,650 with 62 segmented forms, 21 staff cells, 15 lymphocytes, and 2 eosinophils per 100 cells. Several platelet counts varied from 1,750,000 to 2,780,000, the normal for the method being 240,000.

She was readmitted in June, 1948, 7 years later, because of a Colles's fracture produced by a fall. The patient stated that she was allergic to tomatoes and chocolate. The liver was enlarged 2 fingerbreadths downward, and the spleen was enlarged considerably. Her blood pressure was 100/80 mm. of Hg. The red blood cell count was 4 millions; hemoglobin, 12.5 gm.; white blood cell count, 13,400, with 42 segmented forms, 27 staff cells, 6 juveniles, 2 myelocytes, 14 lymphocytes, 5 monocytes, 2 eosinophils, and 2 basophils per 100 cells. Platelets were 250,000.

On her third entry in April, 1949, she complained of malaise, cough, a fever of 102° F., and substernal chest pain. Blood pressure was 118/60. There was slight ankle edema. The patient was dyspneic and had a productive cough. There was a non-tender, freely movable, subcutaneous nodule in the left supraclavicular region. Red blood cell count was 2.81 millions; hemoglobin, 9.3 gm.; white blood cell count, 12,100, with 81 segmented forms, 8 staff cells, and 11 lymphocytes per 100 cells; platelets were 496,000.

Her last entry was in October, 1949, with an additional complaint of weakness. Blood pressure was 130/76. Both lung bases were dull to percussion and had moist râles. The abdomen was distended and showed a fluid wave. Liver and spleen were enlarged. Red blood cell count was 3.04 millions; hemoglobin, 10.9 gm.; white blood cell count 18,400, with 70 segmented cells, 14 staff cells, 12 lymphocytes, and 4 monocytes per 100 cells; platelets, 470,000; serum protein, 4 gm. per cent; albumin, 2.2 gm. per cent; globulin, 1.8; icterus index, 8; cephalin flocculation, 1 plus. Straw-colored fluid (3600 cc.) was removed from the peritoneal cavity. The patient became weaker and complained of generalized pain before her death.

Necropsy was performed 5 hours after death. The body was emaciated but well developed. It weighed 110 lbs. The abdomen was distended. There was edema of the labia and lower extremities. Several subcutaneous nodules were present in the left supraclavicular region, right breast, chest, back, and arms. The nodules varied from 2.5 to 6 cm. in diameter. They were firm, adherent to the skin, and on section were dirty gray and irregular in outline. The adipose tissue of the peritracheal region, mesentery, omentum, peripancreatic, perinodal, perirenal, and periadrenal regions was light yellow-gray studded with minute, irregular, white-gray areas. The pericardial fat presented a similar picture. The left internal jugular vein was thrombosed. The spleen weighed 725 gm. The cut surface was deep red with multiple hemorrhagic areas. The follicles were not apparent. The pulp was fairly firm. The liver weighed 1,850 gm. The capsule was thick, measuring 0.5 to 0.7 cm. and was light to dirty gray. The portal triads and the blood vessels were surrounded by yellow-white areas 2 to 7 mm. thick. The central veins were dilated and red. The submucosa of the small and large bowel was thick and of a dirty gray-white color and studded with minute yellow-white areas. The tibial marrow was yel-

low-white with areas of gray and deep red. The rib and sternal marrow presented a similar picture.

Microscopic Examination. Tissues were fixed in 10 per cent formaldehyde and in Zenker's solution and stained with hematoxylin and eosin, Sudan III for fat, van Gieson's mixture, and with Masson's trichrome stain. The subcutaneous nodules showed extensive fibrosis of the adipose tissue with areas of necrosis involving fat cells. There were areas of inflammation composed of lymphocytes, neutrophilic polymorphonuclear leukocytes, macrophages with cytoplasmic vacuoles, and infrequent multinucleated giant cells. The cell membranes of some fat cells were collapsed and in others the nuclei were centrally placed. Some of the fat cells accepted the fat stain only partly, as was true, also, of many of the cytoplasmic vacuoles within the macrophages. A similar picture was found in the adipose tissue of the peritracheal region, pericardium, omentum, mesentery, intestinal submucosa, and perirenal and periadrenal tissue. The liver capsule and the perivascular and the portal areas of the liver showed a greater degree of fibrosis and hyalinization. The myocardium showed patchy fibrosis. There were emphysema, edema, and passive congestion of the lungs, and marked passive congestion and fatty metamorphosis of the liver. Liver sinusoids contained many macrophages filled with vacuoles. The follicles of the spleen and lymph nodes were markedly decreased or absent. The splenic pulp and the lymph node sinuses contained many macrophages with cytoplasmic vacuoles and there was considerable reticulum cell hyperplasia. The bone marrow of the tibia, sternum, and ribs contained areas of fibrosis, lymphocytic infiltration, macrophages with vacuoles, and fat necrosis with alternating areas of myeloid hyperplasia. The brain showed patchy gliosis and senile arteriosclerosis.

Final Diagnoses. Systemic nodular panniculitis involving subcutaneous tissue, peritracheal, pericardial, perihepatic, perirenal, and periadrenal tissue, submucosa of the gastro-intestinal tract, active and inactive bone marrow, mesentery, and omentum; splenomegaly, follicular hypoplasia and reticulum cell hyperplasia of spleen and lymph nodes, myocardial fibrosis without significant coronary arteriosclerosis, pulmonary emphysema and passive congestion, passive congestion of liver, thrombosis of internal jugular vein, senile arteriosclerosis, and patchy gliosis of the brain.

Case 2

The patient was a white woman, 66 years old, who was followed from 1925 to her death in 1943. In 1925, at the age of 48, she complained of fatigue and "skin trouble"

with questionable subcutaneous nodules. In that year, she had an appendectomy and tonsillectomy. In 1926 her symptoms were fatigue, general malaise, and "colitis." Red blood cell count was 3.68 millions with hemoglobin of 78 per cent and platelets of 323,000 (normal for the method: 240,000).

In 1930 she had a definite, tender, erythematous nodule in the right thigh with crops of more nodules appearing on both legs, back, and abdomen. During the year, some of the nodules became adherent to the skin. She had a fever not in excess of 101° F. Liver and spleen were enlarged. Red blood cell count was 4.22 millions; hemoglobin, 92 per cent; white blood cell count, 8,300. One of the nodules and a lymph node were excised. The tissues were sent to the registry of lymphoid tumors of the Army Medical Museum, as a result of which it was reviewed by eight of the well known pathologists of that period. The diagnoses offered included tuberculosis, syphilis, reticulum cell sarcoma, Hodgkin's disease, infectious hyperplasia, and foreign body reaction. From the descriptive side, the subcutaneous tissue showed necrosis of fat cells, accumulation of lymphocytes, neutrophilic polymorphonuclear leukocytes, plasma cells, macrophages with ingested vacuoles, periarteritis with organization, endothelial proliferation, and edema of vessel walls. The picture was that previously[1-4] and subsequently described as nodular panniculitis, but neither the consultants nor I was aware of this condition in 1930–1931.

The lymph node showed reticular hyperplasia and the presence of many macrophages laden with fat globules and red blood cells as described in necropsies later. The perinodal tissue contained a part of a subcutaneous nodule with the changes of nodular panniculitis.

In 1931 the patient was seen by a Chicago physician who found absence of knee jerks and ankle clonus, fatigue, achylia, a red blood count of 4.6 millions with hemoglobin of 100 per cent, white blood cell count of 6,100, and numerous subcutaneous nodules. A diagnosis of pernicious anemia was made and liver was given.

In 1940 the patient slipped on ice and fractured the neck of the left femur. Her temperature was 98.4° F.; red blood cell count, 3.8 millions; hemoglobin, 70 per cent; white blood cell count, 4,450 to 7,750, with 80 segmented forms, 8 staff cells, 1 juvenile, and 11 lymphocytes per 100 cells; reticulocytes, 0.8 per cent.

She was seen in 1942 and 1943 when she complained of fatigue and tiredness. The radiologist observed an asthmatic contour on a flat film of the chest. Temperature was 99° to 102° F.; pulse, 100 to 130; respirations, 20 to 40. Red blood cell count was 4.21 millions with 72 per cent hemoglobin. White blood cell count varied from 1,200 to 2,800 with 25 per cent segmented polymorphonuclear leukocytes, 44 per cent staff cells, 19 per cent monocytes; platelets were 100,000; hematocrit, 24 per cent. The patient became listless, mentally confused, and died.

Necropsy

The post-mortem examination was performed 9 hours after death. The body was well developed and fairly well nourished. There were multiple irregular subcutaneous nodules on the chest, back, abdomen, and extremities. Some were fixed to the skin and the surrounding tissue, others were slightly movable. They varied in size from 0.4 to 1.8 cm. in diameter. The feet and ankles were slightly edematous. The subcutaneous fat was a dirty yellow with streaks of gray-white. There was fatty infiltration in the right ventricular musculature. The fat was gray-yellow. The lungs were emphysematous and there were some sub-

pleural petechiae. The spleen weighed 1,100 gm.; the follicles were not apparent and the pulp was deep red with regular yellow flecks. The liver weighed 1,950 gm. The cut surface showed dilated central veins and flecks of gray. The periadrenal tissue was a dirty yellow with light red streaks. The bone marrow of the tibia, sternum, and ribs was deep red with patches of gray-white and deep yellow.

Microscopic Examination. The subcutaneous nodules showed abnormal changes confined to the subcutaneous tissue. The abnormalities consisted of:

Irregular fibrosis

Necrosis of fat cells, collapse of walls of fat cells, infiltration of the cells by lymphocytes, macrophages, and multinucleated giant cells

Intimal proliferation of blood vessels, perivascular hyalinization (organization of perivascular inflammatory reaction)

Exudation of inflammatory cells, largely lymphocytes and some plasma cells and monocytes

Presence of a large number of multinucleated giant cells.

The picture was that of the third or atrophic stage of nodular panniculitis. The periadrenal adipose tissue, the perirenal and pelvic fat, the interlobular pancreatic fat, and parts of the bone marrow showed changes of variable degree, which included necrosis of fat cells; collapse of walls of fat cells; presence of inflammatory cells, largely lymphocytes, within fat cells and between the cells; and slight fibrosis. The abdominal lymph nodes were enlarged.

The splenic follicles were either markedly decreased in size or absent. The pulp was filled with macrophages laden with vacuoles, some of which stained for fat. There was considerable hyperplasia of reticulum cells. The liver showed dilated sinusoids filled with vacuolated cells, lymphocytes, and monocytes. There were also areas of necrosis in the central and midcentral zones. The liver cells contained many vacuoles which stained for fat. The lymph nodes showed an extensive reduction of lymphocytes and replacement by macrophages filled with vacuoles and red blood cells.

The heart showed patchy myocardial fibrosis and arteriosclerosis of intramural coronaries. The kidneys showed arteriolar sclerosis with patches of cortical interstitial fibrosis, tubular atrophy, and glomerular hyalinization.

Final Diagnoses. Nodular panniculitis of subcutaneous tissue of trunk and extremities; splenomegaly and hepatomegaly; nodular panniculitis of periadrenal, perirenal, renal pelvic, myocardial, marrow, and pancreatic adipose tissue; extensive hypoplasia of lymphatic tissue

of spleen and lymph nodes; extensive invasion of fat-laden macrophages of splenic pulp, lymph nodes, and liver sinuses; focal necrosis of liver; passive congestion and fatty metamorphosis of liver; myocardial fibrosis; intramural coronary arteriosclerosis; arteriolar nephrosclerosis.

Discussion

The necropsies recorded in the medical literature and those presented here make it possible to follow the progressive changes in the pathogenesis of nodular panniculitis. The primary process consists in

Table II
Pathologic Changes in Systemic Nodular Panniculitis

Pathologic changes		Organs and tissues involved
Panniculitis:	Formation of irregular nodules with the following changes:	Subcutaneous tissue, bone marrow, omentum, mesentery, perivisceral adipose tissue of heart, liver, pancreas, adrenal glands, and kidneys
Stage 1, Onset:	Inflammation of adipose tissue with neutrophilic polymorphonuclear leukocytes, lymphocytes, and macrophages; phagocytosis of fat	
Stage 2, Maturity:	Fat necrosis; collapse of cell membrane, invasion of fat cells by phagocytes and other inflammatory cells; periarteritis and intimal proliferation	Intravisceral: Pancreas Liver Intestinal submucosa
Stage 3, Regression:	Fibrosis of fat; inflammation, multinucleated giant cells, many fat-laden macrophages, periarterial fibrosis	
Enlargement of the organ, focal necrosis, Kupffer cell hyperplasia, fatty metamorphosis, fat-laden macrophages in sinusoids		Liver
Enlargement of the organ, reduction in size or absence of follicles, reticulum hyperplasia, variable number of fat-laden macrophages, decrease in the number of lymphocytes		Spleen and lymph nodes

the destruction of adipose tissue. It is not unlikely that disintegration and phagocytosis of fat cells observed in the lesions are preceded by a chemical transformation of the fat which is rendered inimical and foreign to the body. The failure of some of the fat to accept specific stains and the inflammatory reaction which precedes observable fat disintegration suggest this possibility.

The abnormal changes of the adipose tissue in nodular panniculitis are variable in extent and in degree. The condition may be limited to the subcutaneous tissues. Some 40 cases in the literature demonstrate this limitation. The necropsies of Friedman[27] and of Hanrahan, Ippo-

lito, and Dilworth[39] indicate that the subcutaneous disease is associated also with splenomegaly and hepatomegaly. It is probable that enlargement of the two organs is due to the presence of fat-laden macrophages and hyperplasia of the reticulo-endothelial elements. The term for the disease as it is known now is unnecessarily cumbersome. The name may be simplified to subcutaneous nodular panniculitis in the case of involvement of the subcutaneous tissue only.

That nodular panniculitis varies in severity is apparent from the variable number of subcutaneous nodules and the number of "crops" of lesions. Another factor is the duration of the disease. It may extend for a few weeks, months, or over a period of years.

In addition to the subcutaneous tissue, the disease may involve the perivisceral and even the intravisceral fat of several organs, as well as the omentum and the mesentery. It may also produce focal necrosis of the liver. It may attack the bone marrow with consequent abnormalities of the hematopoietic system. Although the difference between localization to the subcutaneous tissue and systemic involvement is probably a matter of degree, it is suggested that the generalized condition be labeled systemic nodular panniculitis.* Since the disease is usually limited to the subcutaneous tissue and systemic involvement implies the corollary reactions of several organs, the two phases may well be differentiated.

Extension of the disease to perivisceral and intravisceral adipose tissue creates an increased demand for phagocytes and a resultant hyperplasia of the involved organs. This greater and persistent requirement for macrophages may result in a decreased production of other cell types. The marked reduction of lymphocytes in lymph nodes and in the spleen may be due to this process. A second reaction to the increased number of phagocytes is the excessive filling of the spleen, liver, and lymph nodes with fat-laden macrophages, with whatever functional disturbances this type of blockage may imply. Another effect of perivisceral panniculitis is the resultant thickening and fibrosis of organ capsules with loss of elasticity and tendency to constriction. Intravisceral panniculitis may interfere further with the functions of the organ. Focal necrosis of the liver compromises its functions as indicated by the abnormal responses to liver function tests.

Panniculitis with resultant patchy fibrosis of the bone marrow was associated with abnormalities in response on the part of the hemato-

* The inappropriateness of the term panniculitis for a process in regions where there is no panniculus is recognized. However, it is employed in default of a better term and in accordance with established usage.

poietic system. Anemia, leukopenia, appearance of abnormal and immature cells in the blood, and disturbances of platelet production as seen in the two cases presented in this report and by other observers, demonstrate the effects of nodular panniculitis upon the bone marrow.

The pathogenesis of nodular panniculitis gives me little or no help in determining the cause of the disease. Sensitivity to foods in one patient in this report and the radiologic suggestion of an "asthmatic contour" in the other suggest an allergic background. Administration of bromides, iodides, and penicillin in many of the patients reported in the literature throws further suspicion on this mechanism. On the basis of the available evidence, any further interpretation is still more speculative. Adipose tissue may be considered as one of the shock organs in allergy. Antigen-antibody reaction in the adipose tissue of predisposed individuals may be assumed to alter the chemical nature of the fat. Subsequent pathologic changes may result from this alteration. Since the liver is a shock organ, it is not unlikely that in severe instances of the disease, the liver becomes involved. Focal necrosis develops as seen by Mostofi and Engleman[32] and in one necropsy in this report.

The indefinite clinical manifestations of subcutaneous nodular panniculitis include: malaise, fatigability, cough, generalized aching, generalized abdominal pain, chills or chilly sensations, night sweats, occasionally nausea and vomiting; fever of 99° to 104° F.; rapid pulse of 100 to 130; hepatomegaly; splenomegaly; normocytic and normochromic anemia; normal number of white blood cells or leukocytosis or leukopenia with an increase in staff forms and monocytes; normal, increased, or decreased platelets; positive cephalin flocculation test.

In systemic nodular panniculitis more of these symptoms and signs are present and they are more pronounced. Involvement of the bone marrow is followed by leukopenia, thrombocytopenia, and anemia. Extensive panniculitis appears to be associated with an increase in circulatory monocytes. In liver involvement the cephalin flocculation test becomes positive and there is a disturbance in the prothrombin time.

In the patients studied so far, the systemic form has been associated with subcutaneous nodules. Histologic examination of a subcutaneous nodule remains the best diagnostic test for the disease.

Summary

A systemic disorder, hitherto unrecognized, is presented. The condition known as relapsing non-suppurative nodular panniculitis, or

Weber-Christian's disease, had been thought to be confined to the panniculus. Data in this presentation indicate the existence of a systemic disease in which there is involvement of the thoracic, abdominal, perivisceral, and intravisceral adipose tissue. The abnormal changes in the fatty tissue are similar to those observed in the panniculus. Focal necrosis of the liver and the spleen has been found in some of the patients. Involvement of fatty bone marrow results in the interference with the hematopoietic activity and consequent confusion in the diagnosis of blood dyscrasias. Invasion of the lymph nodes, the spleen, and the liver with fat-laden histiocytes produces an enlargement of these organs. The large number of histiocytes, especially in the lymph nodes, has been confused with neoplasia and systemic panniculitis should be considered in the differential diagnosis of lymphomas.

It is suggested that the term for the localized lesion of the panniculus be simplified to subcutaneous nodular panniculitis. Since the condition is known now in the literature as panniculitis, it would be well to retain the name for the systemic disorder. Although panniculitis refers to the subcutaneous adipose tissue, it is suggested that because of previous usage the term systemic panniculitis be used.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

FIGS. 1 to 4. Gross photographs of (*Fig. 1*) omentum, (*Fig. 2*) kidney and adrenal gland, (*Fig. 3*) heart, and (*Fig. 4*) liver of case 2. The omental fat is nodular and shows change in color. The perirenal and pelvic fat of the kidney is thickened and nodular. The periadrenal fatty tissue shows a change in color which is also apparent in the subepicardial fat of the heart and in the perivascular areas of the liver.

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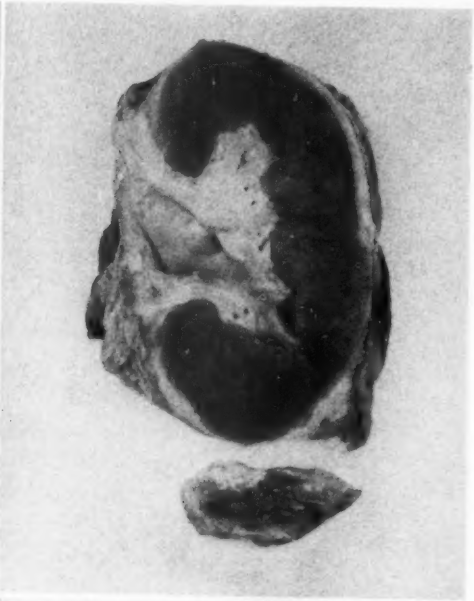

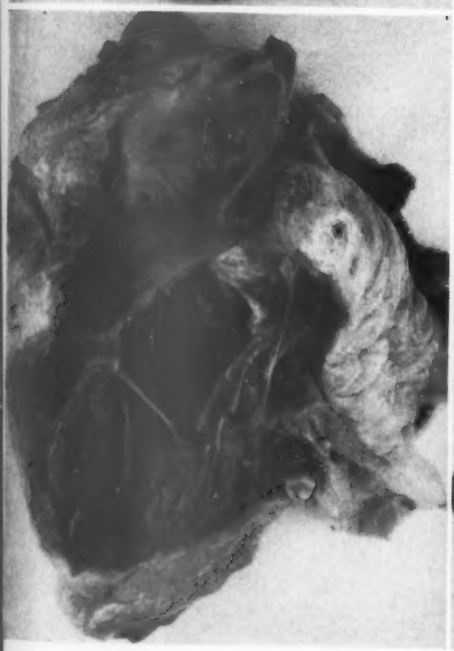

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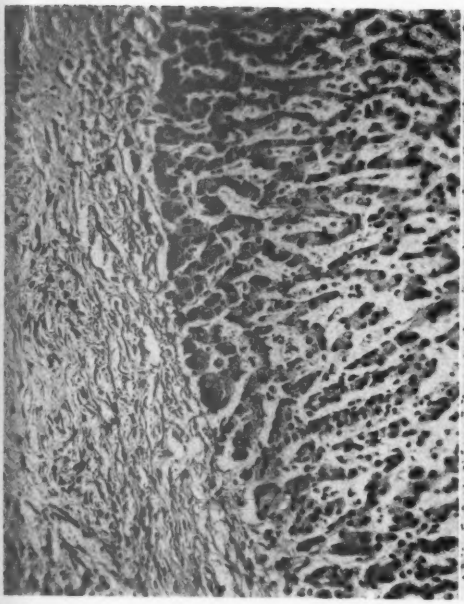
FIGS. 5 to 8. Case 1.

FIG. 5. Liver with perihepatic tissue showing fibrosis, lymphocytic infiltration, and replacement of fat cells.

FIG. 6. Adrenal and periadrenal tissue showing replacement of much of the fatty tissue by fibroblasts and lymphocytic infiltration.

FIG. 7. Bone marrow shows fibrosis, lymphocytes, and only a few fat cells. No myeloid tissue is present.

FIG. 8. Liver showing an area of focal necrosis.



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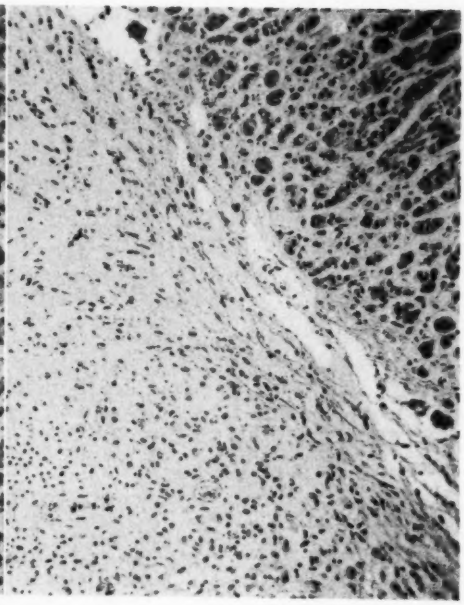

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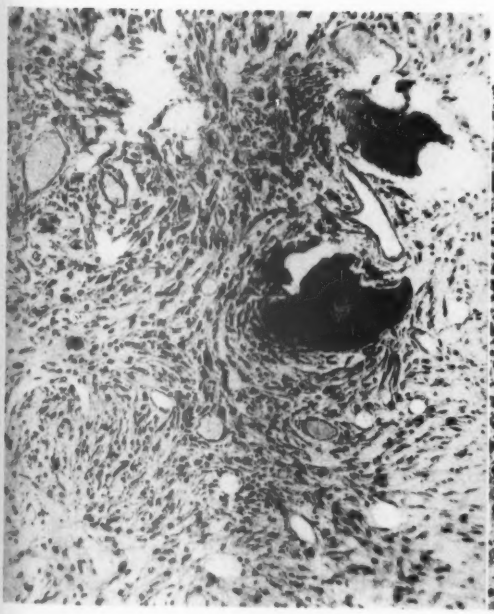

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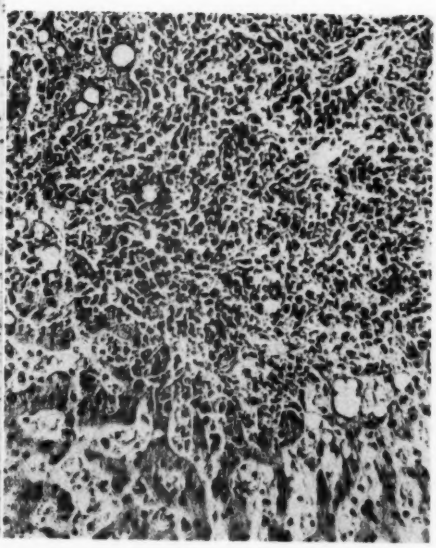

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FIGS. 9 to 12. Case 2.

FIG. 9. Spleen shows considerable hypoplasia of a follicle with very few lymphocytes remaining in the follicle.

FIG. 10. Splenic pulp with many macrophages filled with minute vacuoles, presumably fat. A similar picture is present throughout the pulp.

FIG. 11. Lymph node shows relatively few lymphocytes. The sinuses contain macrophages with ingested vacuoles, some of which take the fat stain. The entire lymph node shows a similar picture.

FIG. 12. Periadrenal tissue shows the second stage of panniculitis with fat cell necrosis, inflammation, and macrophages containing vacuoles, some of which stain for fat.

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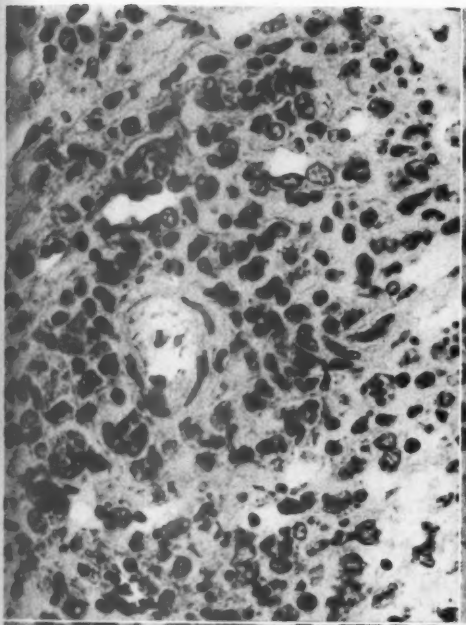

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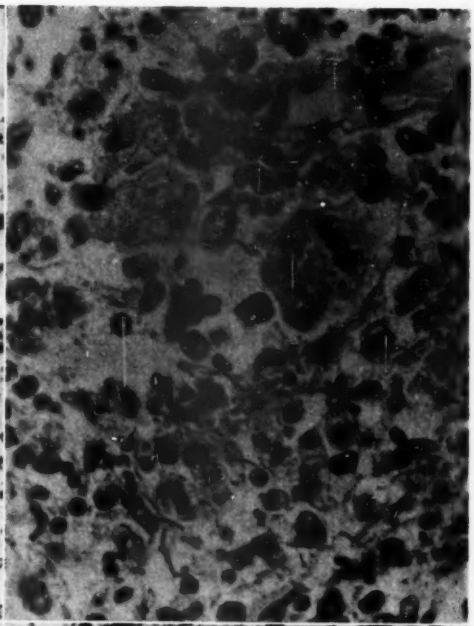

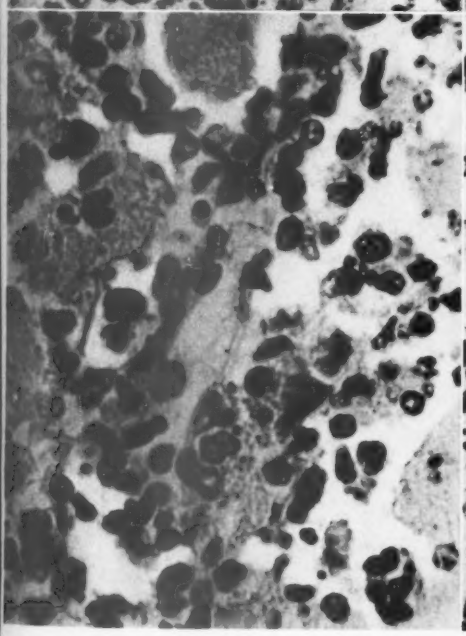

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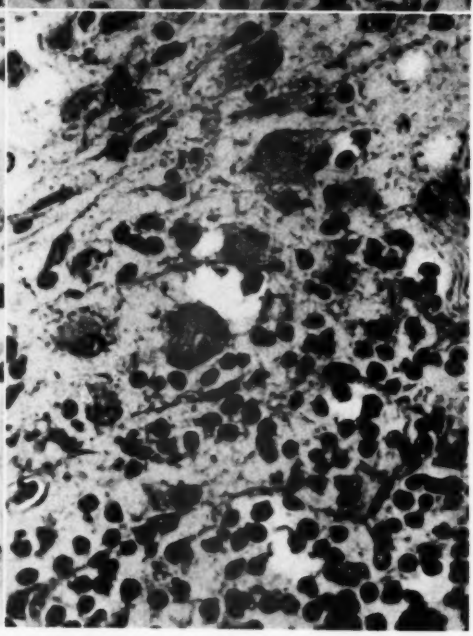

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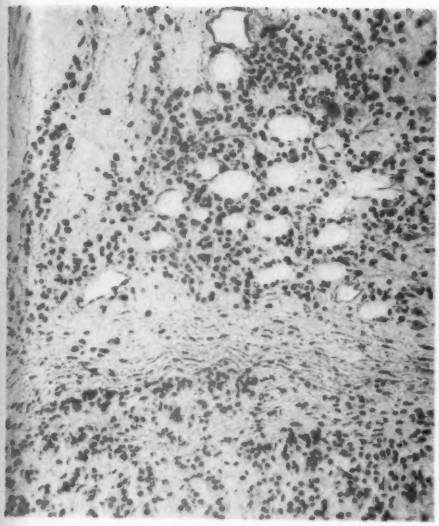
FIGS. 13 to 16. Case 1.

FIG. 13. Panniculitis. First stage shows inflammation of adipose tissue with some inflammatory cells invading fat cells, rupture of walls, and collapse of some of the fat cells.

FIG. 14. Case 1. Panniculitis. Third stage (Fig. 3 may be seen for second stage). There is extensive fibrosis, lymphocytic infiltration, and partial destruction of many fat cells.

FIG. 15. Case 2. Panniculitis. Third stage. Multinucleated giant cells filled with vacuoles, some of which take the stain for fat.

FIG. 16. Case 2. Panniculitis. Third stage. Endothelial proliferation of artery, edema of wall, and organization of adventitia and perivascular area.



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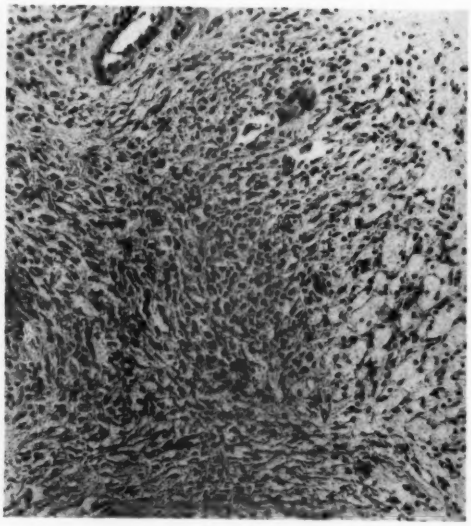

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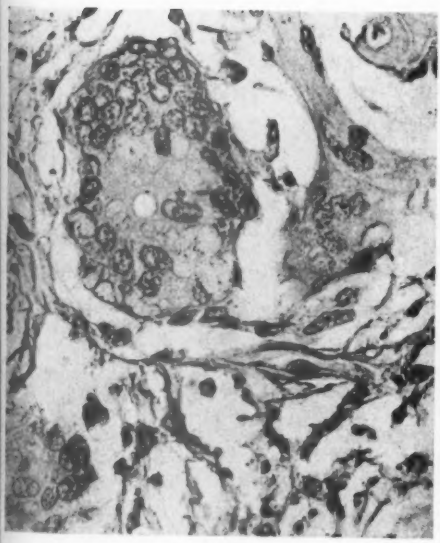

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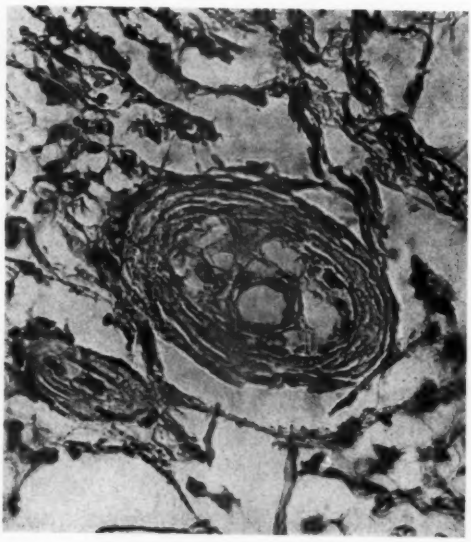

16

DISSECTING ANEURYSM OF THE MIDDLE CEREBRAL ARTERY ASSOCIATED WITH MIGRAINE SYNDROME *

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Dissecting aneurysm of the cerebral arteries, unlike dissecting aneurysm of the aorta, is an exceedingly rare lesion. A review of the literature disclosed only three recorded instances in the last 30 years.[1-3] That such a lesion may be associated with the migraine syndrome might be anticipated as the migraine syndrome is generally considered to have its morphologic basis in focal vasoconstriction, dilatation, and edema of cerebral arteries.[4] Migraine syndrome has been reported in association with other types of cerebrovascular disease but has not been reported in association with dissecting aneurysm.

It is the purpose of this report to (1) record a case of dissecting aneurysm of the middle cerebral artery occurring in a white female, 27 years old, afflicted with severe migraine syndrome; (2) to correlate the clinicopathologic observations to show a relationship of the mechanism of the migraine syndrome as the precipitating factor in the formation of dissecting aneurysm in this case; (3) to review previously reported instances of dissecting aneurysm of the cerebral arteries; (4) to discuss dissecting aneurysms of the aorta in regard to dissecting aneurysms of the cerebral arteries; (5) to review reported instances of vascular disease associated with migraine syndrome to which reference may be made.

Historical Review

Poppen[1] reported two instances of dissecting aneurysms of the cerebral arteries occurring in a series of 143 surgically treated intracranial aneurysms. In one case the lesion was surgically excised and the angiogram and specimen are illustrated in his report. The angular branch of the middle cerebral artery was affected. The other involved the medial trunk of the middle cerebral artery and the vessel was not excised, as it was considered that removal would leave the patient severely incapacitated. Thus this case was not proved, but was diagnosed on the basis of angiograms. Ligation of the internal carotid artery was performed with complete relief of symptoms over an 8-year period. No other details were given. Poppen stated he was unable to find reference to this type of aneurysm in the literature.

Dratz and Woodhall[2] reported a case of traumatic dissecting aneu-

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rysm of the left internal carotid, anterior cerebral, and middle cerebral arteries. The patient was a female, 21 years of age, who was struck by an auto while riding a bicycle. She developed hemiplegia and died a few days later. A tear was found in the intima of the internal carotid artery with a dissecting aneurysm which occluded the channels of the middle and anterior cerebral vessels, leading to thrombosis.

Ramsey and Mosquera[3] reported a dissecting aneurysm of the middle cerebral artery occurring in a white male, 47 years old. This had ruptured producing a massive subarachnoid hemorrhage. Microscopic studies of the artery disclosed marked arteriosclerosis, cystic medial necrosis, focal calcification, and lymphocytic infiltration. These authors, also, stated that they were unable to find any case report of dissecting aneurysm of the cerebral arteries. Hamby[5] referred only to Dratz and Woodhall's case[2] and Dandy[6] made no mention of dissecting aneurysm.

In regard to earlier literature, of which a complete review is beyond the scope of this report, it is of interest that Kaufmann[7] (1929) stated that true dissecting aneurysms frequently occur in the small cerebral vessels. The basis for this statement was the detailed report of Ellis,[8] who, in 1909, reviewed the problem of spontaneous hemorrhage, in a paper presented to the Pathological Society of Philadelphia. This report was based on the study of 20 miliary aneurysms in 31 brains from cases of spontaneous hemorrhage observed in Professor Ludwig Pick's laboratory in the Friedrickshain Hospital, Berlin. He concluded that the lesion of the intracerebral arteries in cases of spontaneous cerebral hemorrhage was primary in the intima, beginning, apparently, in the elastic layer and was simply arteriosclerosis. Progressive involvement of the media and adventitia leads to weakening and rupture. In some cases a circumscribed portion of the wall may give way and permit blood to pass between the coats of the vessel, forming the so-called dissecting aneurysm. Both rupture and dissecting aneurysm were followed by false aneurysms, though this did not occur in every instance. The false aneurysms were called miliary aneurysms. It is clear that Ellis considered the fundamental change to be arteriosclerosis and that this led to rupture and thus cerebral hemorrhage. It is indeed strange that little mention of dissecting aneurysm is made after Kaufmann (1929). The reader is referred to Ellis' review for interesting references to earlier studies.

In these reports no mention is made of the occurrence of the migraine syndrome. That migraine syndrome could be a factor in precipitating dissecting aneurysm of the cerebral arteries might be

anticipated, for it is generally considered that this syndrome has its morphologic basis in local vascular alteration of the cranial and cerebral arteries. Occurring with this are certain psychosomatic functional components and possibly a stress mechanism. The changes occurring in the arteries are described as vasoconstriction followed by vasodilatation; if this is prolonged and severe, edema, thickening, and rigidity of localized segments of cerebral arteries occur.[4] It would thus seem reasonable to expect that in severe instances focal hemorrhage into the edematous wall with dissection and separation of layers or fibers in a localized segment, followed by compression occlusion of the lumen, would result. This complication has not been produced experimentally or described at necropsy in any reported case in so far as I am able to determine.

Report of Case

L. D. was a white housewife, 27 years old, who entered Lutheran Hospital on September 5, 1952, because of severe, right-sided facial and retro-ocular pain which began 16 hours before admission. Eight hours after the onset she noted a "pins-and-needles" sensation in both arms and legs, weakness in both hands, and numbness of her tongue. She had had similar headaches without the peripheral symptoms for several years. These occurred four or five times a year and always on the right. The attacks were acute and were most severe at the onset, with a gradual diminution of pain until subsidence in about 36 hours. Vertigo was often present at the onset but tinnitus or visual symptoms were never associated, although occasionally nausea and vomiting were. There had been no prodromal symptoms. There was no history of trauma. She was without symptoms between attacks. There had been three episodes in the previous 8 weeks. She had been told by several physicians that she had migraine headaches and had been taking a caffeine ergotrate preparation which gave her no relief.

Past Medical History. Thyroidectomy had been performed at another hospital 3 years previously for Hashimoto's disease. Since the operation she had noted less frequent headaches. She had been taking 10 grains of thyroid extract daily but continued to feel lethargic and weak, tired readily, became short of breath on moderate exertion, and had recently noted slight ankle edema. There had been a weight gain of 27 lbs. since the thyroidectomy. She also had had an appendectomy, measles, mumps, chicken pox, and scarlet fever, and had borne 2 children. There were no gastro-intestinal or genito-urinary complaints.

Physical Examination. Temperature was 38° C.; pulse, 64 per minute; respirations, 22 per minute; blood pressure, 118/80 mm. of Hg. The patient was a well developed, well nourished, white female, lethargic and confused. The head, eyes, ears, nose, and mouth were negative. The neck was negative except for a well healed thyroidectomy scar. The chest was clear to percussion and to auscultation. The heart was not enlarged and there was no arrhythmia. The abdomen was negative except for a well healed right lower quadrant scar. Vaginal and rectal examinations were negative. The reflexes were weak and slow to respond.

Laboratory Studies. Red blood cell count, 3.88 millions; white blood cell count, 9,500; hemoglobin, 11.2 gm. or 72 per cent. Bleeding time, 1¼ minutes; clotting time, 3½ minutes. Blood urea nitrogen, 9 mg. per 100 cc. Prothrombin time, 16.8

seconds or 95 per cent of normal. Kline serologic test for syphilis, negative. Spinal fluid showed 2 white blood cells (one lymphocyte and one neutrophil) and 5 red blood cells per high-power field. A repeat spinal fluid examination showed 100 red blood cells and 26 white blood cells (7 lymphocytes and 19 neutrophils) and the protein was 25 mg. per 100 cc. Urinalysis was not performed.

Hospital Course. The patient was given 100 mg. of demerol every 4 hours as needed and 1 grain of phenobarbital twice daily. She was restless, nauseated, and vomited periodically. Slurred speech, urinary incontinence, flaccid paralysis of the left arm and leg, coldness of the left leg, and continuation of the headache were noted during the first 24 hours after admission. A lumbar puncture at that time revealed an initial pressure of 340 mm. of water. This was reduced to 210 mm. of water. On September 8, 1952, at 8:30 a.m., the pulse rate was 50 per minute, respirations were 10 per minute, corneal reflexes absent, and the patient had urinary incontinence. Later that day she was semicomatose but reacted to light stimuli. She could move her limbs and a 2 plus knee jerk was elicited in both legs. The pulse rate remained slow. Auscultation revealed extrasystoles. The respirations were shallow and slow. A second lumbar puncture disclosed an initial pressure of 600 mm. of water which was slowly reduced to 260 mm. of water. The cerebrospinal fluid was clear. There were cyanosis, weak pulse, and deep respiration. The patient died 30 minutes after the second lumbar puncture.

Necropsy Findings

At necropsy (no. 1172) the brain weighed 1300 gm. The cerebral hemispheres showed flattening of gyri and narrowing of sulci throughout. The entire right parietal lobe and a portion of the right frontal lobe were soft and pale yellowish grey. The right middle cerebral artery, 1 cm. from its origin, was enlarged, firm, stiff, and bluish red for a distance of 2 cm. Transection disclosed no visible lumen. The wall was firm and dark red. The aneurysmal dissection extended along the first two branches for a distance of 1.5 and 2 cm., respectively (Fig. 1). There was no appreciable arteriosclerosis and there was no rupture or subarachnoid hemorrhage. The vessels of the circle of Willis had an average anatomical distribution and there were no anomalies. There were no saccular (congenital) aneurysms in the circle or in any of the branches.

Microscopic studies of the right middle cerebral artery (Figs. 2 and 3) showed the wall to be infiltrated with a large mass of red blood cells with dissection of the subintimal layers and focal dissection of the media. The hemorrhage involved approximately one half the circumference of the wall. The internal elastic lamina appeared intact. No tear in the intima could be found. There was no medial necrosis or cystic degeneration of the type observed in the aorta with dissecting aneurysm. There was no evidence of previous damage, such as hemosiderosis or fibrosis. A slit-like lumen of variable size was present and in none of the sections was there thrombus formation. It was consid-

ered that the lumen was occluded by compression during life and was visible in the microscopic sections because of shrinkage following processing. Microscopic sections of the right parietal and frontal lobes of the brain showed changes typical of a recent infarct.

The heart weighed 320 gm. and was not remarkable. There was no valvular disease. The coronary arteries and aorta showed only slight arteriosclerosis. The other viscera were not remarkable. There was no ascites or hydrothorax.

Discussion

The occurrence of dissecting aneurysm of the cerebral arteries without associated trauma, arteriosclerosis, hypertension, or recognizable chronic medial disease as precipitating etiologic agents must indeed be rare, as this has not been reported in the medical literature during the past 30 years.

The relationship of dissecting aneurysm to the migraine syndrome in this case is noteworthy and heretofore not described. The mechanism of the migraine syndrome is generally considered to be related to an initial short period of local vasoconstriction of cerebral arteries followed by a long period of distention. Ergotamine tartrate is widely used with good success as a specific therapeutic agent in this syndrome by reason of its vasoconstrictor effect, which reduces the distention and amplitude of the arterial pulsations. Those factors which reduce the amplitude of pulsation decrease the headache and vice versa. Wolff[4] has made an extensive study of the vascular changes occurring with the migraine syndrome and has shown that thickening or edema of the affected artery may follow sustained vasodilatation of several hours' duration. The artery becomes firm and rigid in contrast to the usually easily collapsible cerebral arteries. This patient's symptoms were always right-sided and the lesion was located on the right. There was no history of trauma and there was no hypertension. The final attack was clearly of greater severity than the patient had previously experienced and required hospitalization. The syndrome began as did the previous ones, was of 16 hours' duration before admission, and there occurred during the course of the episode progression of symptoms from initial right-sided facial and retro-ocular pain to "pins-and-needles" sensations in both arms and legs, weakness in both hands, and numbness of the tongue. This was followed, during the first 24 hours in the hospital, by lapse into a semicomatose state, slurred speech, urinary incontinence, and flaccid paralysis of the left arm and leg. The pulse and respirations became slower and the spinal fluid pressure elevated. The spinal fluid was free of blood. It was apparent

clinically that acute vascular occlusion of the right middle cerebral artery and cerebral edema had occurred. There was relentless progression of the process to the stage of irreversible massive necrosis of the right cerebral hemisphere in the distribution of the middle cerebral artery. From the clinical standpoint the relationship of migraine as the initiating factor in the course of the disease seems entirely reasonable.

The necropsy observations are of the utmost importance in considering whether there was a relationship in this case between the migraine syndrome and dissecting aneurysm. The absence of specific disease in the involved region or elsewhere, such as congenital vascular anomaly, appreciable arteriosclerosis, chronic arteritis, cystic medial necrosis of the type observed in the aorta in dissecting aneurysm, or traumatic injury to the head which was not known clinically, lends support to the concept of a strong relationship. In addition, there was no morphologic evidence in organs such as heart and kidneys that hypertension may have existed. There was no hypertrophy of the heart and no arteriolar nephrosclerosis or other renal disease.

The dissection extended for 2 cm. and likewise along two branches for a distance up to 2 cm. The subintimal and medial hemorrhage and dissection had produced compression occlusion of the artery with resultant development of an infarct of the brain. Edema of the media probably was masked by the hemorrhage. Thus it seems likely, on the basis of the clinical course and the necropsy observations, that in this case there was a distinct relationship between the migraine syndrome and the development of the dissecting aneurysm.

The pathogenesis of dissecting aneurysm of the aorta has been recently presented by Gore[9] who, with Seiwert,[10] studied 85 fatal cases and reviewed the literature. Dissection in the aorta is dependent on an idiopathic degenerative change in the media associated with an inadequate reparative reaction characterized by an increase in the number of vasa vasorum, a mild inflammatory reaction, and the presence of variable amounts of myxomatous tissue. The aneurysm begins by rupture of one or more of the vasa vasorum into the weakened media with formation of a hematoma which splits the media apart. An intimal tear is not a necessary initiating factor and was not present in 23 of the cases. Hypertension is frequently noted clinically.

One of the fundamental changes in dissecting aneurysm of the aorta, namely, chronic idiopathic degenerative change in the media, was not present in this case. Also, the mass of blood in the wall is mostly subintimal. Thus the initiating factor is different apparently in the cerebral arteries, at least in this case. This lends further support to

the concept of localized acute vascular alteration, such as occurs in migraine, as a basis for the dissection. Once the dissection has started, the process is the same as in the aorta with the exception that the cerebral arteries are of such a diameter and composition that compression occlusion may readily develop whereas this would not be expected to occur in the aorta.

Dunning[11] reviewed the literature and found 7 instances (including his case) of migraine associated with intracranial or extracranial vascular accidents. All patients were 18 to 37 years of age at the time of the first symptoms and were in normal health except for migraine. There were 11 vascular accidents, one of which caused death. There were 10 instances of hemorrhage, 7 of which involved the eye. In 3 cases there was cerebral hemorrhage and in 2 of these bloody spinal fluid was obtained. The third disclosed massive subarachnoid hemorrhage at necropsy. There was one retinal infarct. On the basis of this review Dunning concluded that the changes in the caliber of cranial blood vessels, known to occur during attacks of migraine, were probably predisposing factors in hemorrhage and occlusion.

There have been several reports associating migraine with saccular (congenital) aneurysm of the cerebral arteries, and some examples of this association have been confirmed surgically or at necropsy. Frankel,[12] in a review article, recorded 3 cases of saccular aneurysm in which there was a definite change in the severity and character of the headache with what he considered to be permanent dilatation of a congenitally weak point in the arterial wall or dilatation of a minute aneurysm. Further change in the headache followed rupture or massive dilatation of the aneurysm.

Summary

A dissecting aneurysm of the right middle cerebral artery occurred in a white female, 27 years old, afflicted with severe migraine syndrome. The dissecting aneurysm produced compression occlusion of the artery with resultant infarct of the right parietal and frontal lobes of the brain.

A review of the literature disclosed no similar previously reported case and only three proved instances of dissecting aneurysms of the cerebral arteries were found. One was removed surgically, one was the result of trauma, and one occurred in association with severe arteriosclerosis. None was associated with migraine.

It is considered that the basic processes are different in this case than in the pathogenesis of dissecting aneurysm of the aorta, and reference is made to other reported instances of migraine syndrome asso-

ciated with saccular aneurysm, rupture of cerebral arteries, and occlusive disease.

It is considered that in this instance the focal vascular alteration occurring in migraine syndrome acted as the immediate precipitating factor in the formation of the dissecting aneurysm.

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LEGENDS FOR FIGURES

FIG. 1. Gross photograph of the inferior surface of the brain. The dissecting aneurysm involves a segment of the right middle cerebral artery and branches. The circle of Willis is normal. There is no evidence of arteriosclerosis.

FIG. 2. Right middle cerebral artery. There is a wavy intact internal elastica beneath which is a mass of blood forming a dissecting aneurysm involving one half the circumference of the wall. The lumen present is due to shrinkage and was not visible in the fresh gross specimen. No thrombus is present. × 12.

FIG. 3. Right middle cerebral artery. Higher magnification of a portion of Figure 3 to illustrate the wavy internal elastica, massive hemorrhage in subintimal layers, and focal hemorrhage in outer media. × 96.

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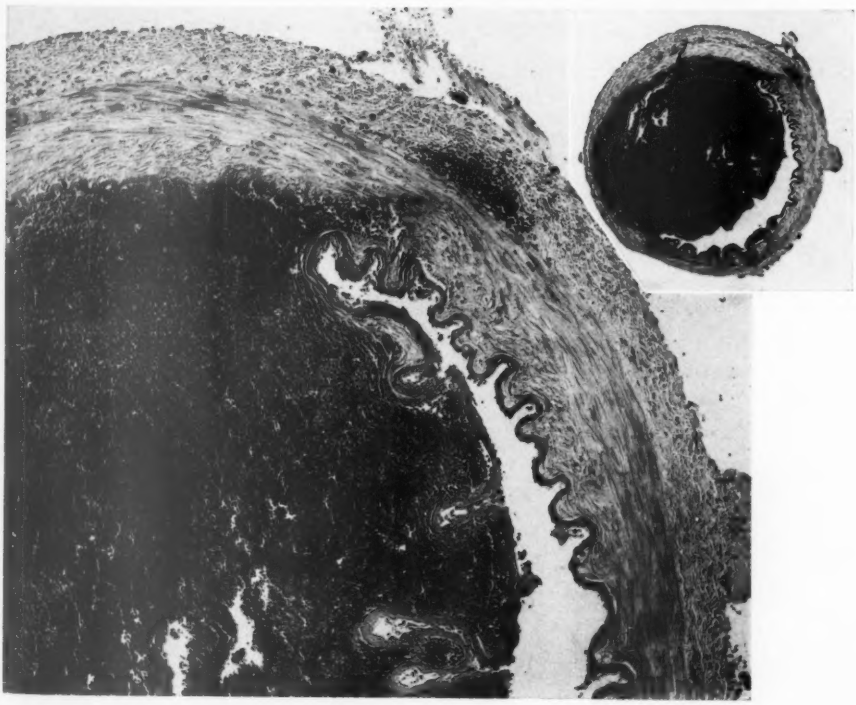

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THROMBOSIS AND PANCREATIC CARCINOMA *

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Although it represents a minute facet of a major clinical problem, there is sufficient interest in the curious occurrence of phlebitis and resistance to anti-coagulant therapy with cancer to consider whether the newer knowledge of the clotting mechanism suggests a reasonable explanation.[1] The simple two-stage schema of Morawitz[1a] which sufficed for two generations of medical graduates has been amplified enormously. That there are still unsolved problems seems high-lighted by the differences between the specialists in this field.[2] It is quite widely recognized that the cancer most frequently associated with this complication originates in the pancreas.[1,3] Furthermore, the correlation is sufficiently strong with lesions of the body and/or tail to be of diagnostic value.[4] Recently, Wright[1] has stated that in his experience the position of the neoplasm within the pancreas was of no importance in the occurrence of intravascular coagulation. Since his opinion is at variance with the expressions of others,[3,5-7] it seemed appropriate to attempt to resolve the discrepancy by a review of available pathologic material. The seemingly minor issue could very well furnish the key to the riddle, as will be seen. The findings which are listed in Table I are not statistically impressive by themselves, but deserve credence since they substantiate the results of Sproul's more inclusive meticulous survey.[3] It was her review of 15 years ago which had emphasized the greater incidence of thrombosis when the pancreatic carcinoma arose in the body or tail. The preponderant evidence does indicate that neoplastic involvement of the pancreatic head is not as frequently associated with thrombosis as when the site of origin is the body or tail.

None of the various ideas proposed as an explanation for this situation seems adequate. Although Sproul[3] and others[8,9] were unable to find any histologic difference between the types of carcinoma occurring in the head and elsewhere in the pancreas, the suggestion has been made[10,11] that the clotting tendency is an effect of the release of coagulative factors from the tumor into the circulation. Mucus-producing columnar cell carcinomas were singled out as the source of such agents,

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yet microscopic evidence of mucin formation occurs in the growths of ductal origin which form the majority of tumors of the head as well as the body and tail of the pancreas.[9,12,13] The frequent occurrence of jaundice with lesions of the head and the more prolonged course of malignant disease of the body or tail have been suggested as factors explaining the differing incidence of thrombosis.[9] However, the proposal fails to account for the even more striking disparity of intravascular clotting when carcinomas of the tail (or body) are compared with other visceral neoplasms[3] in which neither jaundice nor comparative length of survival are factors. Most recently, Wright[1] cautiously mentioned that he had observed progressive elevation of serum alkaline phosphatase in two cases of silent pancreatic carcinoma afflicted with persistent phlebitis. Were that a factor, however, thrombosis would be more frequent with osteogenic sarcoma and Paget's disease of bone, for example, than it apparently is. Finally there is obviously no merit to the suggestion that tissue destruction which occurs with all cancers, releases thromboplastin in the case of pancreatic neoplasms.

TABLE I
Thrombosis and Carcinoma

	Total number	Cases with thrombosis	
		Number	Per cent
Necropsies, 1944 to 1951*	1618		
With malignant neoplasia†	144	28	19.4
Primary carcinoma of pancreas	9	4	44.4
Involving head	5	2	40.0
Body and/or tail	4	2	50.0
Secondary carcinoma of pancreas	14	7	50.0

* Salt Lake County General Hospital.

† Cases of leukemia and lymphoma, which may be complicated by a hemorrhagic state, and of tumors of the central nervous system, arbitrarily, were not included among the tabulated cases of malignant neoplasms.

If one may accept that there is indeed a differing incidence of thrombosis with localization of carcinoma in the head or elsewhere in the pancreas, a reasonable explanation may be deduced. As a rule carcinoma of the head produces ductal obstruction and secondary atrophy of virtually all acinar elements. On the other hand, proximal portions of the gland retain their morphologic integrity when the neoplasm lies distally. Accordingly, it is significant that Sproul[3] had found an anomalous duct permitting normal acinar tissue to persist in two of her three cases of carcinoma of the head associated with thrombosis. The position of the pancreatic neoplasm is important, therefore,

only to the extent that it permits survival of appreciable quantities of intact glandular tissue. It has already been mentioned that a particular histologic type of pancreatic carcinoma cannot be correlated with an increased clotting tendency. Reference to Table I demonstrates that carcinoma of various origins (Table II), as long as it fulfils the criterion of infiltrating functional parenchyma, is as frequently complicated by thrombosis as is primary pancreatic cancer.

The very diversity of the neoplasms associated with thrombosis

TABLE II

Thrombosis as Observed in Necropsies on Patients with Secondary Carcinoma of the Pancreas

Primary site	Number	With thrombosis	Primary site	Number	With thrombosis
Stomach	6	5	Prostate	1	0
Lung	3	0	Ovary	1	0
Cervix	2	1	Cecum	1	1
Total				14	7

seems to rule them out as a possible source of thromboplastic secretion. Quite uniformly, however, microscopic examination demonstrates a reactive zone surrounding the tumor where the acini and ducts of the pancreas are dispersed, and to some extent disrupted, by edema and leukocytic infiltration as well as by cellular invasion and growth (Figs. 1 and 2). In essence, the tumor bed consists of inflamed rather than normal pancreas. The process is slow, smouldering and progressive, fed by the aggressive nature of the cancer which it attempts to constrain. That this is related to the mechanism underlying the coagulative tendency may be suspected, since Miller *et al.*[9] have found a direct relation between the invasive character of the tumor and the frequency of complicating thrombosis. Moreover, the converse—paucity of multiple thrombosis with benign (non-invasive) pancreatic tumors—had been demonstrated more than a decade previously by Sproul.[3] It would seem fruitful, therefore, to inquire further into the significance of the zone of reactive pancreatitis.

Accompanying pancreatitis to a degree that its recognition is of diagnostic value, there is a rise of serum lipase and amylase.[14,15] Devastation of the gland nullifies the elevation indicating that its origin is not destroyed pancreas but disrupted and still functional glandular tissue.[16] Tumors of the pancreas[7,15] also have been found, though less frequently, to produce elevated serum levels of these enzymes. Since the functional capacity of pancreatic carcinoma usually is far inferior to that of the normal gland, the zone of reactive pancreatitis surround-

ing the tumor is the source of the rise in circulating enzymes. With total destruction and atrophy of the gland, which occurs so frequently with primary carcinoma, this change does not occur; accordingly, one can readily understand that the serum enzyme changes would be less consistent with cancer than with pancreatitis. That necrosis, vascular lesions, and hemorrhage which are present in the "classic" type of acute pancreatitis[17] are not found in the reactive zone about a pancreatic neoplasm merely reflects the abruptness and massiveness of the former—a quantitative rather than a truly qualitative distinction. However, neither the elevation of amylase nor of lipase permits an explanation of the clotting tendency. But since parallel quantities of trypsin are produced and extravasated in the zone of glandular disruption, an inquiry into the effects of the proteolytic enzyme seems pertinent. Hitherto, relatively little attention has been given to trypsin levels because the other enzyme determinations, just as informative, are far simpler technically and because blood normally contains a large quantity of antitryptic substances.[18] Nevertheless, Howard[19] observed the presence of active trypsin in the peritoneal fluid of patients with acute pancreatitis. Rush and Cliffton[20] noted that patients recovering from pancreatitis showed a considerable elevation of serum antiproteases entirely comparable to the rise observed in animals following the injection of trypsin. Furthermore, an abnormal release of trypsin into the circulation can produce a severe coagulative disturbance which deserves closer scrutiny.

Trypsin given intravenously has a thromboplastic effect.[21,22] Given rapidly, it causes massive intravascular coagulation and death. With slower injection, much larger quantities may be tolerated quite readily but produce a prompt but transitory depletion of prothrombin and fibrinogen. With frequent repetition of such doses, it is virtually possible to cause defibrination and to produce thereby a hemorrhagic state. Intravascular thrombi are not observed in the latter situation; the fibrin evidently becomes widely and imperceptibly dispersed over the entire vascular tree[22] in a manner most conducive to fibrinolysis. Trypsin itself is thrombolytic as well as thromboplastic,[21] an effect which it may well augment by activating the serum profibrinolysin, plasmin.[20,23] In naturally occurring disease processes, aside from the bite of certain venomous snakes, there is no analogue to the massive clotting produced by the rapid intravenous administration of trypsin. The irritative processes affecting the pancreas do not release enzymes in such an overwhelming fashion. The slower release of trypsin in disease processes provides the organism with time to augment the anti-

tryptic substances which are normally present in the serum. It is this circumstance which presumably protects it from the clot-promoting effects of the enzyme in acute pancreatitis. A rise in the level of blood antitrypsin occurs with great consistency following the onset of pancreatitis or the administration (intravenous) of trypsin, so that its measurement has been urged as a diagnostic procedure.[24,25] The determination is made by measuring the capacity of the plasma to inhibit the action of a standard thrombin preparation under controlled conditions.[26] Innerfield, Angrist, and Benjamin,[24,25] although aware[27] that they were actually measuring antitryptic activity, have used the designation antithrombin in conformity with Quick[26] who had devised the procedure some years previously. However, the relationship, if any, of trypsin-inhibiting "antithrombin" to the naturally occurring substance still remains to be elucidated.

Exceptionally in pancreatitis, presumably progressing too rapidly for adequate body response, a hemorrhagic tendency may be observed.[28] This would appear to be the analogue of the state produced in animals by frequent administration of trypsin which depletes all the plasma-clotting factors. Failure of the antitrypsin mechanism may also result from a defect in production. Innerfield, Angrist, and Boyd[29] have shown low values of antithrombin to be correlated with hepatic failure and have suggested that the liver normally produces a protein precursor which requires trypsin for its activation. Two other recent reports similarly have described subnormal plasma antithrombin levels with advanced hepatic disease.[30,31] However, before concluding that such a finding predisposes to a thrombotic state it will be recalled that with hepatic failure there are also primary deficiencies of prothrombin, fibrinogen, and even platelets.[30] Actually it is not uncommon to observe a hemorrhagic diathesis with terminal hepatic failure. For our purposes, we must postulate a rather isolated functional defect entailing reduced antithrombin-producing capacity with lesser involvement of fibrinogen and prothrombin formation. There are other well recognized examples of isolated defects of liver function. Prothrombin deficiency is produced deliberately in current medical practice by interfering with its synthesis in the liver. The effectiveness of antabuse for alcoholism stems from its action upon a specific liver function.[32] Recently, too, accelerator globulin deficiency seems to have resulted from impaired hepatic function with widespread, malignant disease.[33]

How do all these seemingly unrelated phenomena permit an understanding of the clotting tendency observed with certain tumors of the pancreas? Cancer, in contrast to acute pancreatitis, is a protracted

process with a course measurable in months rather than days. With malignant lesions embedded in functional pancreatic tissue, there is a slow and unremittent release of trypsin into the circulation. While at any moment its magnitude probably does not approach that observed with acute inflammatory lesions, it is continued over a much longer period. As already outlined, there is a compensatory rise of antitrypsin, but over a prolonged interval marked by progressive debilitation, one can readily accept a failure of this mechanism. As Abels and associates[34] have demonstrated for the gastro-intestinal tract particularly, the nutritional disorder which so frequently accompanies cancer may have a detrimental effect on liver structure and presumably on its function. It is suggested, then, that it is a failure of the antitrypsin mechanism which accounts for the clotting tendency observed with the tumors under discussion. The net effect supplements the influence of vascular injury, stagnation, and other clot-promoting circulatory factors which only too often are adequate *per se* to result in thrombosis.

One morphologic finding deserves further comment since it suggests the action of an unopposed thromboplastic agent. While the majority of the thrombi were venous and did not differ in localization from those complicating a variety of clinical conditions, Thompson and Rodgers[7] noted a high incidence of arterial thrombi. In two of three examples of carcinoma of the tail of the pancreas with thrombosis in my series and in four of Sproul's[8] five cases there were polypoid fibrin thrombi attached to otherwise normal aortic or mitral valve leaflets (Fig. 3). They had formed along the line of apposition and their occurrence on the systemic side of the circulation, with its more forceful valvular closure, suggests that they had been initiated by ordinarily innocuous endothelial injury at the site of impact. Furthermore, under circumstances favoring the formation of fibrin within the circulation, the motility of the leaflets provides them with a harvesting effect analogous to the action of glass beads in defibrinating blood in the laboratory.

Finally, lest it seem confusing that a lowered level of prothrombin should be found in the face of tendency to thrombosis, it should be recognized that the depletion is a secondary effect resulting from hyperutilization rather than a primary defect of formation.

Summary

An explanation has been suggested for the curious relationship between carcinomas of the pancreas and thrombosis. The key factor would appear to be the presence of functionally intact but morphologically disrupted glandular tissue as the tumor bed. The frequency

with which obstructing neoplasms of the head of the gland lead to atrophy explains the lesser incidence of intravascular coagulation with that localization. Metastases within the pancreas from tumors of various origins affect the coagulative mechanism in an identical fashion, thereby reaffirming the lack of significance of the histologic type of the neoplasm.

The clotting disturbance stems from the release of trypsin from the disrupted glandular tissue of the tumor bed. The thromboplastic effects of trypsin ordinarily are neutralized by the presence of antitryptic substances within the serum. Their titer, as determined by measurement of plasma antithrombin, rises considerably in acute pancreatitis. However, a mechanism which is operative in an acute short-lived process may fail when the stress which has invoked it continues over a long period. Progressive debilitation which occurs with cancer increases the possibility of such failure; should it occur, the continued release of trypsin from the tumor bed would lead to the occurrence of intravascular coagulation. Naturally, such a mechanism would merely supplement the circumstances which contribute to thrombosis in other disease states. Frequent involvement of the arterial side of the circulation, particularly the heart valves, seems to be the only anatomical respect in which this thrombotic process differs from the more common forms of thrombosis.

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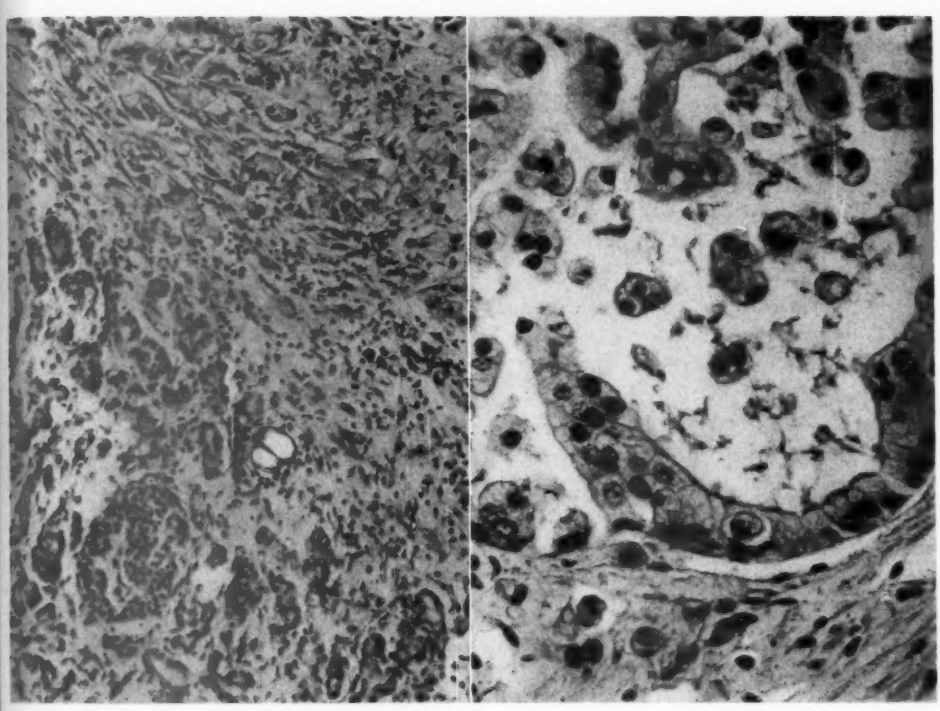
[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. Inflammatory reaction involving the pancreatic parenchyma at the border of an adenocarcinoma primary in the organ. Hematoxylin and eosin stain. × 95.

FIG. 2. Detail of the adenocarcinoma illustrated in Figure 1. Of note are the neoplastic duct-like structure and the clear cytoplasm of the cells, which stain positively for mucin. Hematoxylin and eosin stain. × 335.

FIG. 3. Polypoid fibrin thrombus attached to the distal margin of an otherwise normal aortic valve leaflet. Hematoxylin and eosin stain. × 3.5.



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MORPHOLOGIC CHANGES OF EXFOLIATED CELLS IN EFFUSIONS OF CANCER PATIENTS FOLLOWING INDUCED VIRAL INFECTIONS

Preliminary Observations *

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Studies with transplantable tumors in animals have indicated that several viruses possess the capacity of inhibiting tumor growth.[1-4] Following observations of Koprowski and Norton[4] that, in certain mouse tumors, West Nile, Ilhéus, and Bunyamwera viruses displayed oncolytic properties, experimental clinical trials were undertaken in patients having advanced inoperable neoplastic disease in order to determine whether viruses might also demonstrate an anti-neoplastic effect.[5-7] More recently, it has been reported that Bunyamwera and West Nile viruses will inhibit the growth of certain mouse ascites tumors,[8,9] and that the study of the exfoliated cells in the ascitic fluid is a useful method for the demonstration of this oncolytic effect.[8] Therefore, it seemed of interest to study the ascitic and pleural effusions of patients undergoing experimental clinical virus treatment in order to determine whether the Papanicolaou smear technique would demonstrate any effect upon the exfoliated cells.

The findings described are based on a limited number of cancer patients treated with Egypt 101 and Egypt 21 strains of West Nile virus,† and found suitable for cytologic studies. Because of the scarcity of human material available for a clinical investigation of this type, I feel justified in reporting my observations.

Material and Methods

Patients. The 6 patients studied were selected from a much larger group of advanced cancer patients hospitalized and undergoing experimental virus treatment in the virus research unit of Memorial Center for Cancer and Allied Diseases, New York City. They were chosen because they had peritoneal or pleural effusions graded as class V by

* This study was supported in part by a Control Project Grant to the Papanicolaou Cytology Laboratory, from the National Cancer Institute, National Institute of Health, U.S. Public Health Service.

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† The viruses referred to in this paper as the Egypt *strains* of West Nile virus were isolated from blood of persons in Egypt[10] and are apparently identical with West Nile virus.

the Papanicolaou technique. The age, sex, and diagnoses were based on final histopathologic reports except for case 6 in which only radiologic and cytologic reports were available. Five patients received the Egypt 101 strain of West Nile virus and one, case 1, received the Egypt 21 strain of West Nile virus. Virus was administered by a single inoculation of a crude suspension of infected mouse brain. The intramuscular route was used with the exception of one patient (case 4), to whom the virus was administered intraperitoneally. The dose was 2 to 4 cc. of a 20 per cent mouse brain suspension. When titrated intracerebrally in mice the suspension gave a 10^{-5} to 10^{-7} LD_{50} titer.

Preparation of the Smears. The pleural and peritoneal fluids were obtained by needle aspiration. Approximately 30 cc. of the freshly collected fluid was mixed immediately with an equal amount of 50 per cent ethyl alcohol and promptly centrifuged for ½ hour at 1500 r.p.m., according to the technique used in Papanicolaou's laboratory. The supernatant fluid was discarded. Four smears were made from each sediment, fixed wet in equal parts of ether and 95 per cent ethyl alcohol for at least ½ hour, and stained by the standard Papanicolaou stain 267.[11]

Microscopic Examination. The microscopic examination of smears consisted of two steps. (1) Each of the four smears was screened for cancer cells and the specimen was rated according to Papanicolaou's classification as to the content of conclusive neoplastic elements. (2) Differential counts were made, by counting at least 100 cells in each of two slides from every set of four smears.

In examining the smears after inoculation of the virus, special attention was directed toward the following characteristics:

1. The relative number of cancer cells
2. The number of necrotic cells in relation to the number of cancer cells
3. The relative number of cells in karyorrhexis and/or cells with cytoplasmic inclusions of phagocytized nuclear material.

Results

Cytologic observations prior to the induced infection

One or two samples of the pleural and/or peritoneal fluids from each patient were studied prior to the inoculation of virus. The smears from the peritoneal fluids of 2 patients (cases 1 and 4) were characterized by a strikingly irregular distribution of clusters of malignant cells and great variation in the number of cells in these clusters. Figures 1 and 2 illustrate such clusters. In contrast to these, Figure 3

illustrates the uniformly distributed discrete malignant cells observed as a rule in smears prepared from the peritoneal fluids of mice with Ehrlich ascites tumor.[12]

The presence of dubious cells, the neoplastic nature of which was often suspected but not conclusive according to the cytologic criteria of malignancy, was encountered in some patients and will be discussed. Figure 4 illustrates such "doubtful" cells, as seen in pleural fluid of case 6. The cells shown in Figure 4 have relatively large hyperchromatic nuclei, which vary somewhat in shape as well as in the distribution of chromatin, and therefore fulfill certain cytologic criteria of malignancy. However, their discrete arrangement and their similarity to mesothelial cells in respect to size and shape favor their being mesothelial in nature. These cells were counted as a separate type and referred to in Table I as unclassified.

The presence of occasional necrotic cells, mitotic figures and phagocytes was apparent in some smears prior to the infection, but karyorrhexis was observed only exceptionally before inoculation of the virus.

REPORT OF CASES

Case 1

C. L. was a man, 62 years old, who had a carcinoma having origin in the gastro-intestinal tract and who was infected with the Egypt 21 strain of West Nile virus (Table I).

Smears of the peritoneal fluid contained 7 to 8 per cent of malignant cells prior to the infection. The percentage of cancer cells decreased on the seventh and twelfth days following the inoculation of virus, but this decrease is probably not highly significant because of the low initial count.

The pre-treatment pleural fluid contained a higher relative number of malignant cells (42 and 74 per cent depending upon the slide) than the peritoneal fluid. Following the inoculation of virus, there was apparently no significant change in the percentage of cancer cells. The appearance of karyorrhexis in malignant cells following infection with the virus, however, might suggest that there was an increase in cellular destruction.

Interesting changes occurred in the percentage of non-malignant cells in the pleural and peritoneal fluids. Histiocytes were twice as numerous as lymphocytes prior to the infection. In specimens taken on days 3, 4, and 6 following inoculation the histiocytic preponderance was even greater, but on the seventh and twelfth days there was a significant reversal of the histiocyte-lymphocyte ratio (Table I).

TABLE I

Differential Cell Counts in Serial Specimens of Pleural and Peritoneal Effusions from Four Patients Treated with West Nile Virus

	Days after virus	Percentage of cell types					Remarks	Virus recovery	
		Malignant cells	Histiocytes	Polymorphonuclear leukocytes	Lymphocytes	Mesothelial cells		Blood	Fluid
Case 1									
Ascitic fluid	−8	8	54	11	26	1		+	+
		7*	54	1	36	2			
	3	11	77	2	9	1		+	+
		2	77	1	15	5			
	7	4	12	2	78	4		+	o
		2	10	9	75	4			
	12	4	15	7	74	o		o	o
Right pleural fluid	−3	42	30	7	16	5			
		74	14	o	5	7			
	4	55	30	4	3	6	2% karyo.	+	+
		67	19	o	3	10	1% karyo.		
	6	65	30	o	2			+	+
		60	19	6	7	7	1% phago.		
	12	79	11	3	5	2	karyo. noted	o	o
		54	23	7	14	2			
	26	81	4	1	13	1		o	o
		59	8	7	24	2			
Case 2									
Ascitic fluid	o	1†	1	1	91†	5	1% degen. cells		
		1	4	o	93	1	1% phago.		
	2	2	2	2	85	8	1% phago.	+	+
		o	4	1	89	6			
	5	o	1	1	96	2		+	+
		o	12	o	82	5	1% multi.		
	7	1	o	1	47	48	3% karyo.	+	+
		1	o	1	76	22		+	+
Right pleural fluid	o	4†	2	1	91†	1	1% phago.		
		2	8	o	89	1			
	1	1	1	1	97	o		+	+
		1	3	1	92	o	2% degen. cells, 1% karyo.	+	+
	6	1	3	3	93	o		+	+
		2	4	1	93	o			
	8	o	22	6	70	o	2% phago.	+	+
	9	o	9	3	84	1	3% phago.	+	+
		1	5	6	88	o			
	12	o	13	2	83	o	2% phago.	+	+
		o	30	2	68	o			
Case 3									
Right pleural fluid	−47	6	38	o	52	1	2% degen., 1% phago.		
		8	40	2	48	1	1% degen.		
	−1	14	48	5	26	7			
		21	31	3	42	1	1% phago., 1% mito.		
	5	8	41	3	45	3		+	+
		4	26	9	56	o	5% degen.		
	8	2	32	8	54	1	3% degen.	+	o
		6	31	3	57	o	3% degen.		
	19	2	25	2	69	2		o	o
		1	48	2	45	2	2% degen.		
	31	4	40	5	48	o	3% degen.		
		4	31	14	49	1	1% degen.		

TABLE I (Cont'd.)

	Days after virus	Percentage of cell types: Malignant cells	Histiocytes	Polymorphonuclear leukocytes	Lymphocytes	Mesothelial cells	Remarks	Virus recovery: Blood	Fluid
Case 6									
Right pleural fluid	−5	8	21	18	44	2	6% uncl. + 1% karyo.		
	1	1	16	21	56	0	6% uncl. + 1% karyo.	+	0
	2	1	14	20	55	0	10% uncl. + 1% karyo.	+	+
	7	1	15	0	79	2	1% uncl. + 2% karyo.	+	+
	9	3	22	3	68	0	4% uncl. cells	0	+
	15	0	9	7	70	2	4% uncl. + 8% karyo.	0	0
Left pleural fluid	−2	1	20	8	6	13	1% mito. + 51% uncl.		
	5	2	34	1	15	2	1% mito. + 45% uncl.	+	+
	12	0	31	3	5	9	1% mito. + 51% uncl.	0	0

* The two rows of data for each specimen indicate results from the two smears of each specimen which were counted. These are presented separately rather than averaged in all cases except for case 6, in order to indicate the variation encountered in such preparations. At least 100 cells were counted from each smear. In one instance (ascitic fluid in case 1, 12th day) only one smear was technically adequate for counting.

† In case 2, cells classified as lymphocytes are considered to be malignant (lymphosarcoma) cells. In addition, cells classified as malignant are cytologically abnormal elements probably of the lymphoid series.

karyo. = cells in karyorrhexis.

phago. = phagocytes with cytoplasmic inclusions of ingested nuclear material.

multi. = multinucleated cells.

degen. = degenerated (necrotic) cells.

uncl. = unclassified cells of doubtful nature: cells suggestively but not conclusively malignant.

mito. = cells in mitosis.

Figure 5 shows a representative high-power view of the smear of the peritoneal fluid on day 7 after giving the virus. Only lymphocytes are seen, although 2 to 4 per cent malignant cells were still present. This may be compared with Figure 1 which shows the peritoneal fluid smear collected prior to the infection. The illustrated cluster of malignant cells is surrounded by non-neoplastic cells among which lymphocytes are not predominant, but intermixed with histiocytes and polymorphonuclear leukocytes.

In this patient, the days during which the percentage of lymphocytes in pleural and ascitic fluids was diminished correspond to those on which virus was isolated from these fluids and from blood. There was no clinical evidence of the virus infection in this patient, except for a slight rise in temperature on the second and third day after inoculation. Neither was there any clinical evidence that the course of the malignant disease was altered during this period except for a fall in the serum alkaline phosphatase from 50.7 Bodansky units before treat-

ment to 39.3 units 1 month after treatment. The patient died of acute gastro-intestinal hemorrhage approximately 40 days after treatment.

Case 2

R. D., a 60-year-old male with lymphosarcoma, was injected with the Egypt 101 strain of West Nile virus. Differential counts of cells from peritoneal and pleural fluids (Table I) revealed a very high percentage of lymphocytes (89 to 93 per cent), which in this patient represented the neoplastic cells. In addition, 1 to 4 per cent of the cells were classified as atypical lymphocytes.* Following virus inoculation, the relative number of lymphocytes did not undergo marked changes until the seventh day when there was a decrease in the percentage of the lymphocytes (47 and 76 per cent) in peritoneal fluid with a corresponding increase in mesothelial cells.† Three per cent of the cells showed karyorrhexis as an indication of cellular destruction. Similar but less marked changes occurred in the pleural fluids. Virus was recovered from pleural and peritoneal fluids and blood on the same days (Table I).

This patient developed fever starting 8 days after virus inoculation, climbing to 103° F. on the twelfth day, and accompanied by concurrent signs of bronchopneumonia which did not respond to antibiotic treatment. The patient died on the twelfth day and necropsy confirmed bronchopneumonia as a contributing factor to death.

Case 3

M. S., a female, 77 years old, who had generalized carcinomatosis from a terminal bronchiolar carcinoma, was inoculated with Egypt 101 strain of West Nile virus. During the 7 weeks' period prior to administration of the virus (Table I), the relative number of malignant cells increased. A group of malignant cells from the pleural fluid collected 1 day prior to the inoculation is shown in Figure 8. Figure 9 illustrates a single malignant cell from pleural fluid of the fifth day, indicating the persistence of neoplastic cells following virus infection. The percentage of malignant cells, however, became progressively lower following virus inoculation. An equally low percentage of cancer cells in

* The morphologic distinction of the neoplastic lymphocytes from those found in the fluids from patients with carcinoma was not feasible.

† That the mesothelial cells had proliferated was suggested not only by their increased relative number, but also by the appearance in the smears of large aggregates of these cells. Figure 6 represents a typical high-power view of the peritoneal fluid smear obtained on the seventh day and should be compared with Figure 7. The latter shows a single mesothelial cell and several lymphocytes in the proportion characteristically seen in the smears of peritoneal fluid of this patient before inoculation of virus.

the specimen collected 7 weeks prior to the viral treatment suggests that this decreased exfoliation may not be very significant.

This patient's temperature spiked to 102.8° F. at 24 hours after virus inoculation but was not significantly elevated thereafter. There were no other clinical signs or symptoms attributable to the virus infection. There was no objective clinical evidence of tumor regression. The patient died 2 months later. Virus was recovered from the specimens of pleural fluid taken 5 and 8 days after administration of virus. There was a suggestive rise in the percentage of lymphocytes, starting on the fifth day after inoculation with virus and continuing thereafter. No significant changes in the percentage of histiocytes were observed in this patient.

Case 4

M. H., a female, 44 years of age, with ovarian carcinoma, had Egypt 101 virus injected intraperitoneally. The irregular distribution of clusters of malignant cells in the peritoneal fluid of this patient made difficult the evaluation of changes in the percentage of cancer cells (Fig. 2). A considerable difference occurred between two smears prepared from the single pre-treatment specimen. Nevertheless, in general the relative number of cancer cells in the peritoneal fluid on and after the seventh day following virus inoculation remained at a slightly lower level than that observed before. A slight and transient decrease in lymphocytes and a correspondingly higher histiocytic count were observed on the second day after the inoculation of virus, and a subsequent increase in lymphocytes was noted on the twelfth day. Figure 10 shows two well preserved cancer cells and several lymphocytes found in the peritoneal fluid of the patient on the 22nd day after inoculation of the virus, when there was a definite increase in the relative number of lymphocytes.

Virus was not recovered from any of the specimens of ascitic fluid examined, nor was it recovered from blood except for one specimen taken 6 days after inoculation which showed suggestive evidence of a very low titer of virus. There was a moderate temperature rise during the week following virus inoculation but no other signs or symptoms attributable to the virus. Failure of the virus to grow in the ascitic fluid cells suggests that the changes in cytologic findings, if significant, were probably unrelated to virus propagation in the peritoneal fluid.

Case 5

Y. N., a 38-year-old female with carcinoma of the breast metastatic to both pleural and peritoneal cavities, was injected with Egypt 101

West Nile virus. The relative number of malignant cells (Fig. 11) in the left pleural fluid did not vary significantly throughout the period of observation. This patient had a temperature of 101° F., prior to virus inoculation and temperature fluctuated between 100° and 103° during the following 10 days. A causal relationship between this fever and the virus inoculation cannot be ascertained. There were no other signs or symptoms attributable to the virus. Virus was demonstrated in blood from the 3rd to the 9th day following virus inoculation, and in all pleural fluids collected on the 3rd through the 13th days. The patient died of respiratory failure on the 21st day.

Case 6

A. P. was a male, 62 years old, who had carcinoma of the stomach metastatic to right and left pleural surfaces. Both right and left pleural fluids were studied. The percentage of definitely malignant cells was low in all fluids throughout the period of observation (Table I). The highest percentage (8 per cent) occurred in the right pleural fluid preceding virus infection. There was a difference between the right and left pleural fluids. In the left pleural fluids there were numerous cells which were suggestively but not definitely malignant. In contrast, fluid from the right pleural cavity had more definitely malignant cells and rarely showed doubtful cells.

The malignant cells observed in this case are illustrated in Figure 12 (right pleural fluid, pre-treatment). The low percentage of malignant cells in these fluids prior to inoculation of virus renders hazardous any interpretation of minor changes. It may be noted, however (Table I), that the relative numbers of cancerous elements in the right pleural effusion were consistently lower after virus inoculation than in the pre-treatment specimens.

The number of cells showing karyorrhexis in the right pleural fluid became strikingly high on the 7th and 15th days after virus infection (2 and 8 per cent, respectively) and their presence was considered somewhat suggestive of increased cellular destruction. Indeed, the appearance of the necrotic cells with broken-down nuclei and with nuclear fragments scattered in part throughout the cytoplasm and in part expelled beyond the cellular borders was quite noticeable in this case. One such cell found in the 7th day sample of the right pleural effusion is illustrated in Figure 13.

The relative number of lymphocytes was much higher in the right pleural fluid than in the left throughout the period of observation. An increase in lymphocytes occurred in both pleural fluids after the infection. Virus was demonstrated in this patient's blood for 7 days

TABLE II
Summary of Changes in the Cytologic Findings

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Summary of Changes in the Cytologic Findings

Case	Patient age and sex	Diagnosis	Fluid	Virus present		Principal cytologic changes			Days of greatest change
				Fluid	Blood	Malignant cells	Lymphocytes	Histiocytes	
				days	*days*				
1	CL 62 M	Adenocarcinoma of G. I. tract	Ascitic pleural	3–6	2–8	Slight decrease No change	Increased Slight increase	Decreased Slight decrease	7,12
2	RD 60 M	Lymphosarcoma	Ascitic pleural	1–10 1–10	1–10 1–10	Decreased* Decreased	Decreased Decreased	Increased Increased	7 12
3	MS 77 F	Terminal bronchiolar carcinoma	Pleural	5	1–7	Slight but progressive decrease	Increased	No change	5
6	AP 62 M	Adenocarcinoma of stomach	Rt. pleural Lt. pleural	1–9 1–9	1–7 1–7	Slight decrease Slight decrease	Increased Slight increase	No change No change	7, 9, 15 12
4	MH 44 F	Adenocarcinoma of pancreas	Ascitic		7	?	Delayed increase	No change	
5	YN 38 F	Adenocarcinoma of breast	Pleural	3–14	3–9	No change	No change	No change	

* In patient RD 60 M, lymphosarcoma, lymphocytes are considered to be the malignant cells.

following inoculation, and in all pleural fluids through the ninth day. The only clinical reaction to the virus infection was a slight elevation of temperature (101.2° F. maximum) during the period of viremia. The patient died at home approximately 3 months after virus treatment.

CORRELATION OF CYTOLOGIC, VIROLOGIC, AND CLINICAL RESULTS

Data from all 6 patients are summarized in Table II. The occurrence of a small but perhaps significant decrease in the relative number of neoplastic elements following the induced infection with Egypt 101 strain of West Nile virus was seen in 2 patients (case 2, lymphosarcoma; and case 3, terminal bronchiolar carcinoma). In the remaining 4 patients there was no definite decrease of cancer cells. Slight increases in karyorrhexis were noted in cases 1, 2, and 6, but the magnitude of these changes was so slight as to make a causal relationship to the virus infection uncertain. There were no consistent changes in frequency of cellular degeneration or phagocytosis of nuclear material of sufficient degree to suggest an effect of the virus infection.

Changes in non-neoplastic cells also occurred during, and presumably because of, the

virus infection. There was an increased percentage of lymphocytes in the effusions of 4 of the 5 patients with carcinoma. In the patient with lymphosarcoma (case 3), the lymphocytes considered to be neoplastic lymphosarcoma cells decreased.

The increase in lymphocytes was first noted between the 5th and 7th days after virus inoculation (cases 1, 3, and 6). It coincided with and extended beyond the period of viremia but did not necessarily coincide with the presence of virus in the serous effusions. In case 4, in which propagation of virus was not demonstrated, an increase in lymphocytes was manifest on the 22nd day. This was preceded by a slight transient decrease in lymphocytes on the 2nd day after inoculation. A similar decrease of lymphocytes preceded an earlier and definite lymphocytic increase in case 1. No definite alteration in lymphocyte count following induced viral infection was noted in the peripheral blood of a larger group of patients reported elsewhere.[7]

Inasmuch as persistent viremia following virus inoculation is a direct evidence of virus propagation, and increased normal lymphocytes in effusions were correlated with viremia in 4 of 5 patients with carcinoma, it would seem to follow that such lymphocytic increase has some relationship to virus propagation.

The reverse effect on lymphocytes in the lymphosarcoma case may indicate an oncolytic action of the Egypt 101 strain of West Nile virus. These findings suggest an ability of this virus to act selectively upon neoplastic cells of the lymphoid type. In attempting to correlate the cytologic observations with the clinical findings one is handicapped by the fact that the patient with lymphosarcoma died too soon to permit evaluation.

In the other patient (case 3, terminal bronchiolar carcinoma) objective improvement was not demonstrable.

Discussion

The present study was undertaken in the hope that the oncolytic properties of the West Nile virus might be demonstrated in man by serial studies of exfoliated cells. Certain problems were encountered which limit the applicability of this method for such clinical investigations.

There is still insufficient knowledge of variations in differential cell counts in smears from serous effusions when no therapy is being given. Comparisons must be restricted to fluids from a single source. For example, right and left pleural fluids in case 6 are not comparable. Percentages of exfoliated cells do not necessarily correlate with the

total number or the condition of cells in metastases. In addition, the subjective factor in identification of individual cells is recognized. The difficulty of making a sharp distinction between definitely and suggestively malignant cells and between mesothelial cells and histiocytes has been mentioned. Confusion in distinguishing between lymphocytes and large, round, hyperchromatic fragments of extracellular nuclear material is also possible. As to the lymphocytes, the fairly constant time of their increase and the small number of cells in karyorrhexis favor the present interpretation.

Summary and Conclusions

The morphologic effects of two strains of the West Nile virus on exfoliated cells in smears from the pleural and peritoneal fluids of 6 inoperable cancer patients were studied by a method of evaluating the percentages of malignant and non-neoplastic cells stained according to the Papanicolaou technic.

A decreased exfoliation of neoplastic cells was noted in 2 patients following inoculation of the virus. One had terminal bronchiolar carcinoma, and the other had lymphosarcoma.

Following viral infection an increase in lymphocytes was noted in the effusions of 4 of the 5 patients with carcinoma.

The use of the Papanicolaou technique to study serial specimens of serous effusions offers, in selected patients, a method applicable to the objective evaluation of therapeutic efficacy.

I wish to acknowledge my indebtedness to Drs. Alice E. Moore and Chester M. Southam for supplying the specimens of exudates and the clinical and virologic data reported herein. I am also indebted to Dr. C. M. Southam for critical revision of the manuscript and to Miss Suzanne Voorhies for photography.

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LEGENDS FOR FIGURES

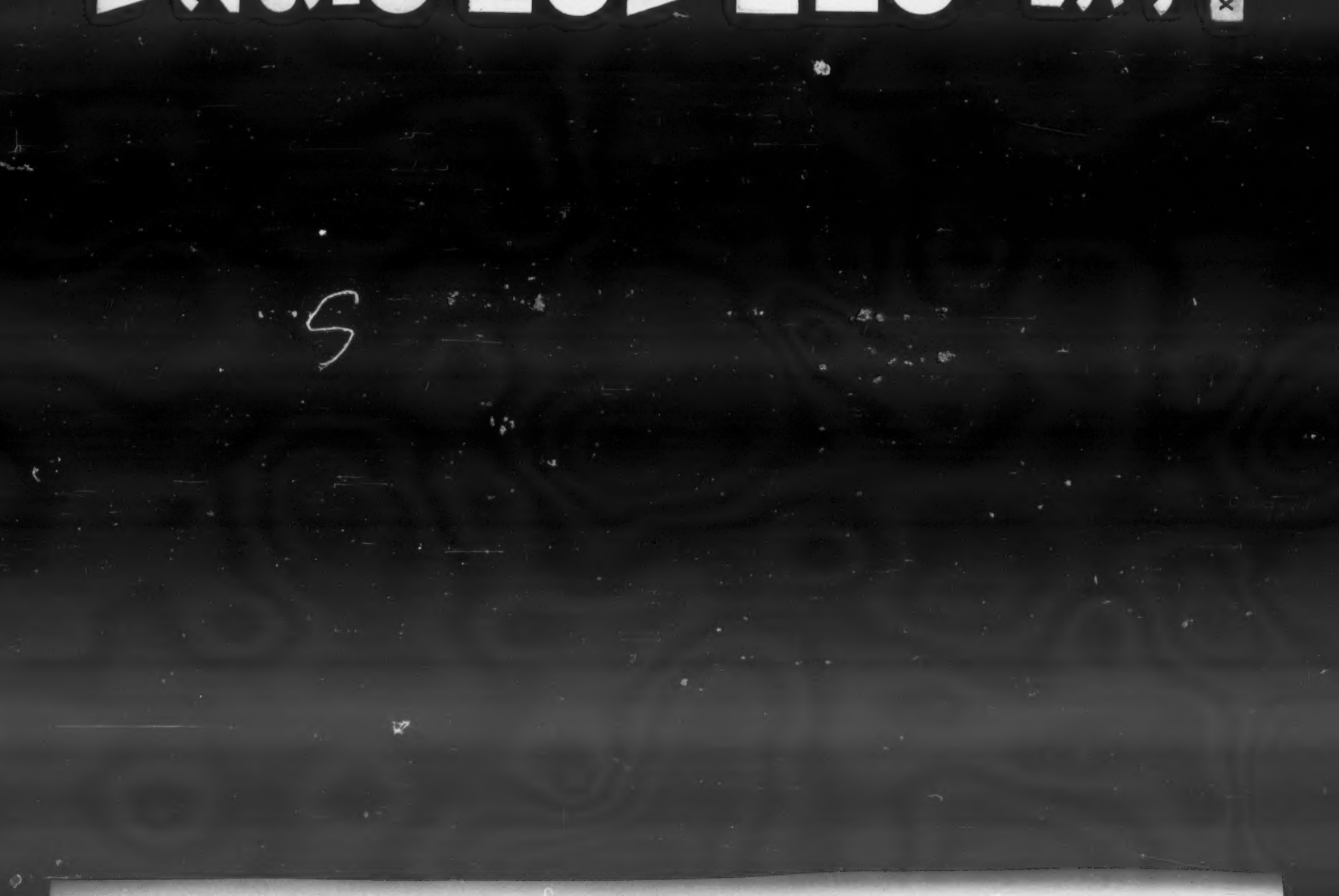
All photomicrographs were made at magnification 600 ×.

FIG. 1. Case 1. Cluster of malignant cells in peritoneal fluid X1829, collected 8 days prior to inoculation of virus.

FIG. 2. Case 4. Cluster of malignant cells in peritoneal fluid X1891, obtained 5 days before injection of virus.

FIG. 3. Discrete and relatively uniform malignant cells in mouse ascites tumor.

FIG. 4. Case 5. Doubtful cells in right pleural fluid X1551, collected on the seventh day following inoculation of virus.



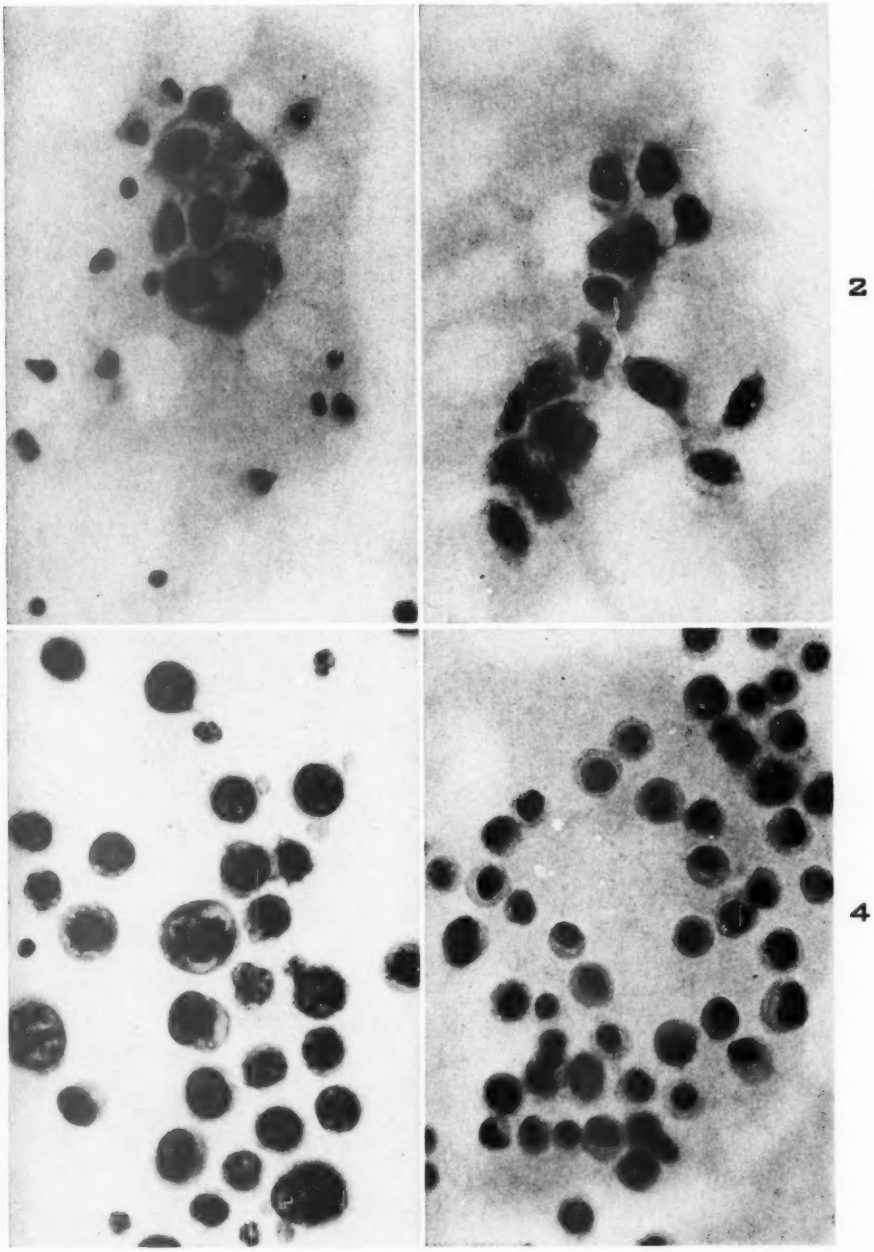

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FIG. 5. Case 1. Lymphocytes in peritoneal fluid X1829, seventh day after injection of virus.

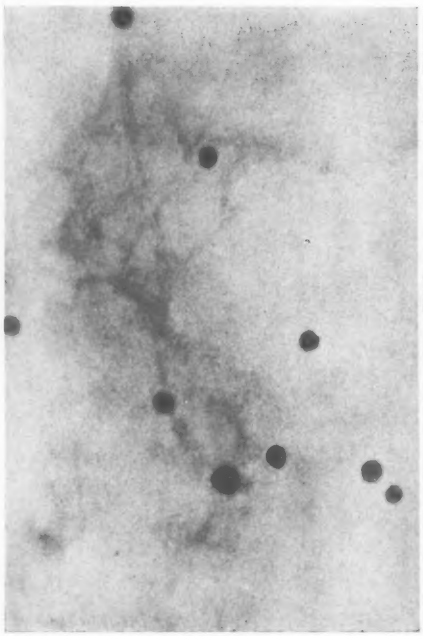
FIG. 6. Case 2. Collection of mesothelial cells in peritoneal fluid X1835, seventh day after injection of virus.

FIG. 7. Case 2. A single mesothelial cell and several lymphocytes in peritoneal fluid X1835, day of the inoculation of virus.

FIG. 8. Case 3. Malignant cells intermixed with various inflammatory cells in pleural fluid X1815, collected 1 day prior to injection of virus.

FIG. 9. Case 3. A single malignant cell and 3 lymphocytes in pleural fluid X1815, collected 5 days after inoculation of virus.

FIG. 10. Case 4. Two malignant cells and several lymphocytes in peritoneal fluid X1891, obtained on the 22nd day after injection of virus.



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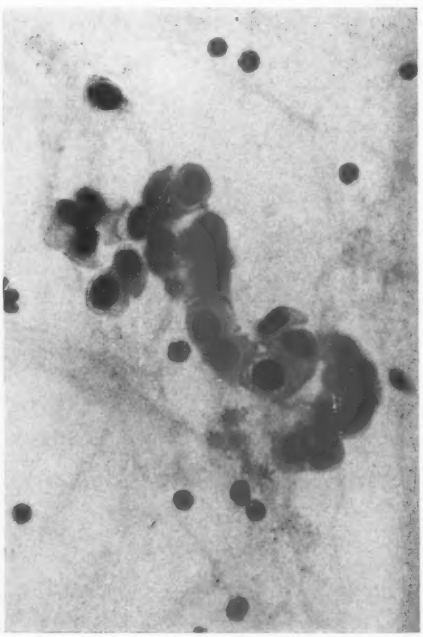

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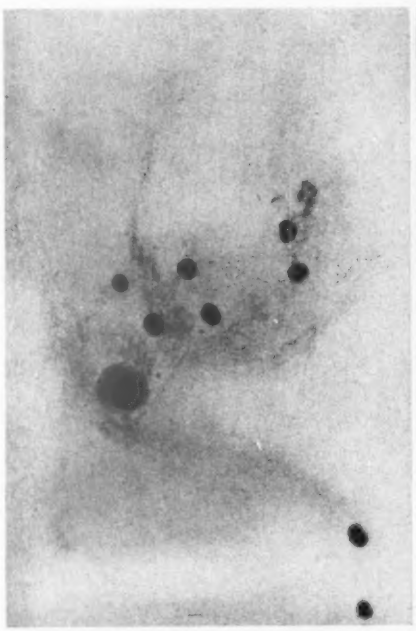

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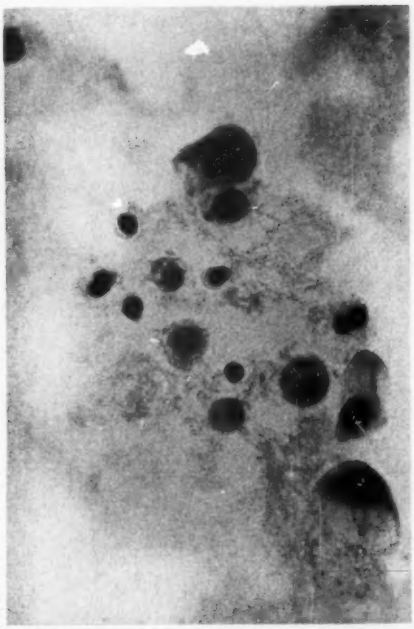

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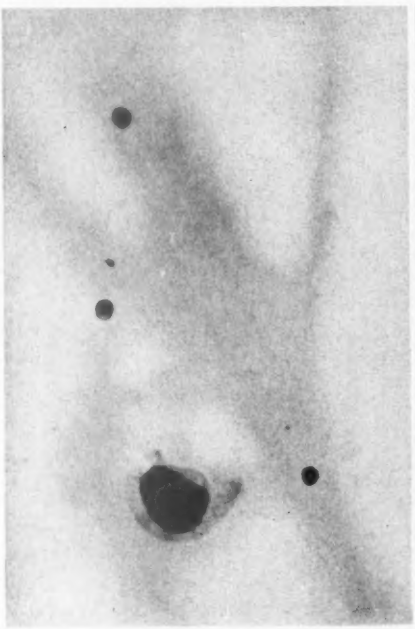

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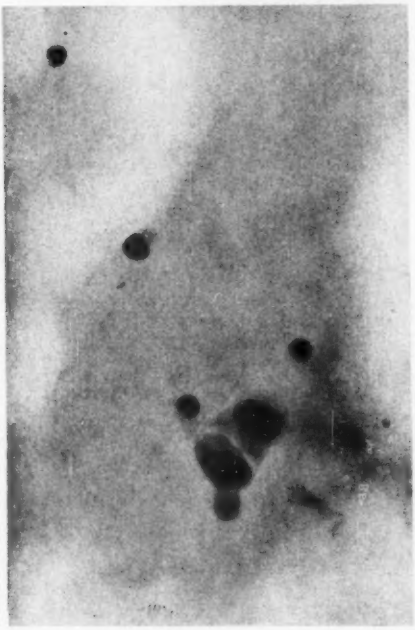

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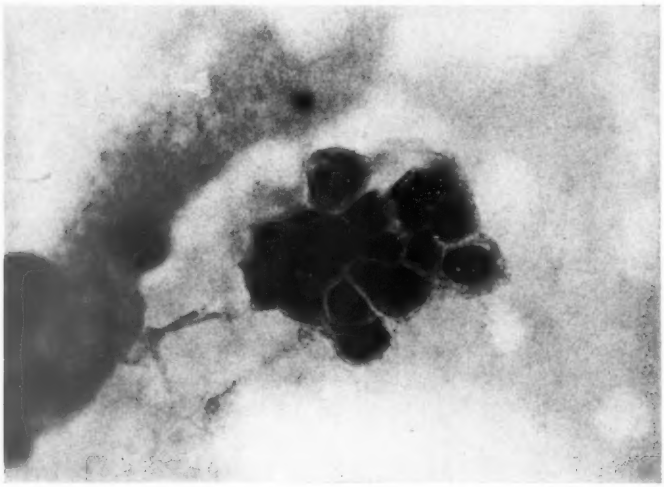
FIG. 11. Case 5. Cluster of malignant cells in left pleural fluid X1551, before inoculation of virus.

FIG. 12. Case 6. Malignant cells in right pleural fluid X1609, prior to injection of virus.

FIG. 13. Case 6. Karyorrhexis in right pleural fluid X1609, 7 days following inoculation of virus.



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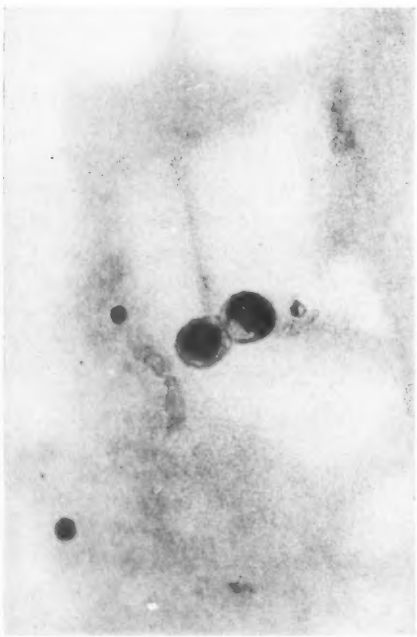

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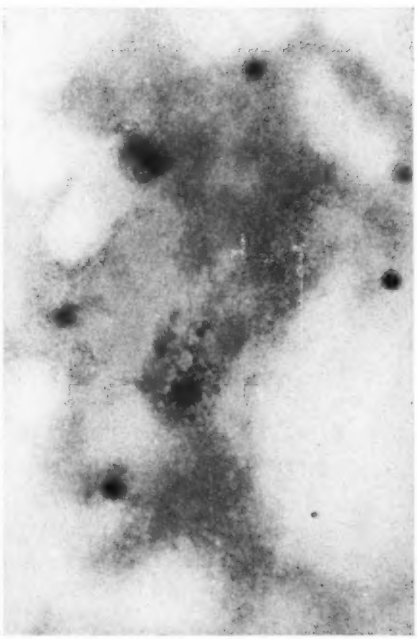

13

OSTEOID FORMATION IN GIANT CELL TUMORS OF BONE*

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Much has been written regarding the nature of giant cell tumors of bone and there have been differences of opinion over practically every aspect of the lesion. For a time there were those who held that this was not a true neoplasm, but a tissue reaction in response to trauma and chronic irritation.[1-4] Long experience with the clinical and pathologic aspects, however, has left no doubt that it represents a rather distinctive neoplasm of bone, the cause of which is as obscure as that which incites any other benign or malignant tumor.[5-7]

It has further been clearly established that the tumor is not an entirely benign growth as was championed by some early writers.[8-10] It displays various degrees of malignancy, such as characterize many tumors, whether derived from epithelium or connective tissue.[11-15] Well documented reports of metastatic giant cell tumors of bone can be found.[16-18]

At present, debate is concerned largely with the histogenesis of the neoplasm, and the theories that prevail can be divided into two general categories. There are some who believe that this tumor arises from non-bone-forming connective tissue of the marrow without attempt at bone differentiation,[19] while others hold that it arises from cells with bone-forming potentiality and that differentiation is toward the bone resorptive phase of bone formation, namely, the formation of osteoclasts.[20-22]

From a study of 13 well established giant cell tumors of bone, it is believed that three histogenetic facts can be demonstrated: (1) The basic cell of the tumor is the mononuclear cell, which may (2) differentiate into osteoclast-like giant cells, or (3) into osteoblast-like cells which form osteoid tissue. These functional differentiations produce little or no change in nuclear appearance and only cytoplasmic fusion in the formation of giant cells.

PRESENTATION OF DATA

In the present study, 13 cases of giant cell tumors of bone from the files of the Hahnemann Hospital were reviewed. In all, the clinical history, age of the patient, location of the tumor, and the radiographic appearance were consistent with the diagnosis of giant cell tumor of

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bone. In all cases, after gross and microscopic examination, this diagnosis was returned by the laboratory.

In general, the unmodified neoplastic tissue consisted of the usual admixture of round and fusiform cells, interspersed with varying numbers of multinucleated giant cells. Small vascular channels were often prominent. Hemorrhage and tumor necrosis occurred occasionally.

In studying this series of cases special attention was given to the presence of osteoid tissue. This finding was noted in 6 of the 13 cases. Careful examination of the osteoid tissue revealed unquestionably that it was being elaborated by the mononuclear tumor cells and did not represent previously normal bone that was undergoing destruction and resorption by the tumor (Fig. 1). At all times these spicules had the immature appearance of newly elaborated bony matrix and frequently were covered by large round cells closely resembling active osteoblasts, undoubtedly representing further differentiation of the mononuclear tumor cells (Fig. 2). Occasionally, beginning calcification of these osteoid spicules was noted (Fig. 3). Cement lines were absent, further serving to indicate that the bony matrix had not been present for any great length of time. The osteoid formation was found within the body of the tumor and did not represent reactive periosteal bone formation. The absence of osteoid tissue in some of the cases may be explained in one of two ways. Either insufficient neoplastic tissue was examined to reveal its presence or there was no osteoid tissue elaborated by those particular tumors. If the latter explanation obtains, it detracts in no way from the osteoid-forming capacity of the mononuclear tumor cells when this capacity is noted in such a high percentage of cases.

In studying these tumors, one is impressed with the close interrelationship of the mononuclear and multinuclear cells. It would be unwise to conclude that they are entirely distinct cell types with different ancestral origins, and yet this type of thinking has, in part, led to the confusion concerning this tumor. It is most probable that the multinucleated giant cells are formed by fusion of the mononuclear cells, a belief that has received the most support in both early and recent studies.[19,23,24] The nuclei of these giant cells are at all times very similar to those of the mononuclear cells, a fact which obtains through all degrees of atypism of the tumor. When irregularity, non-uniformity, and other nuclear changes suggestive of a more aggressive growth are noted in the mononuclear cells, the same changes can also be seen in the nuclei of the giant cells. This is an observation that has been cited by others,[19] and was evident in this series of cases (Figs. 4, 5, and 6). This, in addition to a microscopic appearance strongly sug-

gestive of fusion of the cytoplasm of the mononuclear cells in various parts of the tumor, makes it difficult to believe that formation of these giant cells could be otherwise (Fig. 7). After careful study of this series of cases, we find ourselves in complete agreement.

The additional ability of the mononuclear cells to elaborate osteoid tissue is a function that has been strangely ignored in all writings about this tumor, but which should not go unseen or be ignored because of the more obvious and predominant formation of giant cells. The few who have apparently noted the presence of osteoid tissue have failed to make mention of its significance.[24]

Discussion

It is logical to conclude that the giant cell tumor is derived from cells of bone-forming potential when the basic tumor cell has been shown to have the ability to form osteoid tissue. The formation of multinucleated giant cells by mononuclear cells histologically identical with those elaborating osteoid tissue should not be regarded as something entirely removed from the process of bone formation. Indeed, the close resemblance of these multinucleated cells to the osteoclasts of bone-resorptive lesions as well as their formation from the same cells that are forming osteoid tissue preclude any such attempt. It is generally accepted today that osteoblasts give rise to osteoclasts in normal bone formation.[25,26] Similarly, in giant cell tumors of bone, cells capable of forming osteoid tissue also form multinucleated giant cells closely resembling osteoclasts. The function of osteoclasts is still unproved, but decision whether the cell is a bone resorber or a result of bone resorption is not essential in a discussion of the histogenesis of this tumor. The predominance of multinucleated giant cells in these tumors can only indicate that differentiation is primarily in the direction of osteoclast formation and that the tumor represents an exaggerated resorptive phase of bone formation.

These observations bear directly on the problems of diagnosis of malignancy in giant cell tumors. Jaffe, Lichtenstein, and Portis[19] believed that the stromal mononuclear cells should be most closely scrutinized in appraising the relative malignancy of giant cell tumor. We are in agreement, but it must also be recognized that, because of the mode of formation of the giant cells, they will exhibit many of the changes noted in the mononuclear cells. When these changes are not seen, it probably is because more malignant and consequently more poorly differentiated mononuclear cells display less attempt at giant cell formation. In evaluation of the aggressiveness of this neoplasm,

the degree of attempt at giant cell formation is not to be disregarded. When these cells have poorly defined borders and fuse with the surrounding intercellular stroma, in addition to exhibiting nuclear changes, suspicion should be cast on the future behavior of the tumor (Figs. 4, 5, and 6). These criteria are, of course, evidence of growth of a more poorly differentiated type and are substantially those which are used in the histologic evaluation of the relative malignancy of all tumors. That they are not infallible in appraising potential malignancy, we are sure most pathologists will agree.

Summary

The basic mononuclear cell of giant cell tumors of bone exhibits two functions. The elaboration of osteoid tissue is undeniably bone-formative in nature. It is believed that the more obvious formation of multinucleated giant cells represents an exaggerated resorptive phase of bone formation and that, in reality, these cells are "tumor osteoclasts." It is concluded, therefore, that giant cell tumors of bone are derived from primary bone-forming tissue which may, as in normal bone, produce bone-forming cells or cells concerned with bone resorption. In these tumors the latter predominate.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. Newly elaborated osteoid spicule within a giant cell tumor of bone. Also shown are the surrounding mononuclear stromal cells of the tumor. × 360.

FIG. 2. Osteoid spicule with osteoblast-like cells on surface. The cells merge imperceptibly with surrounding stromal cells. × 360.

FIG. 3. Irregular osteoid spicules being elaborated by a giant cell tumor of bone. One spicule shows the presence of a central area of calcification. × 80.

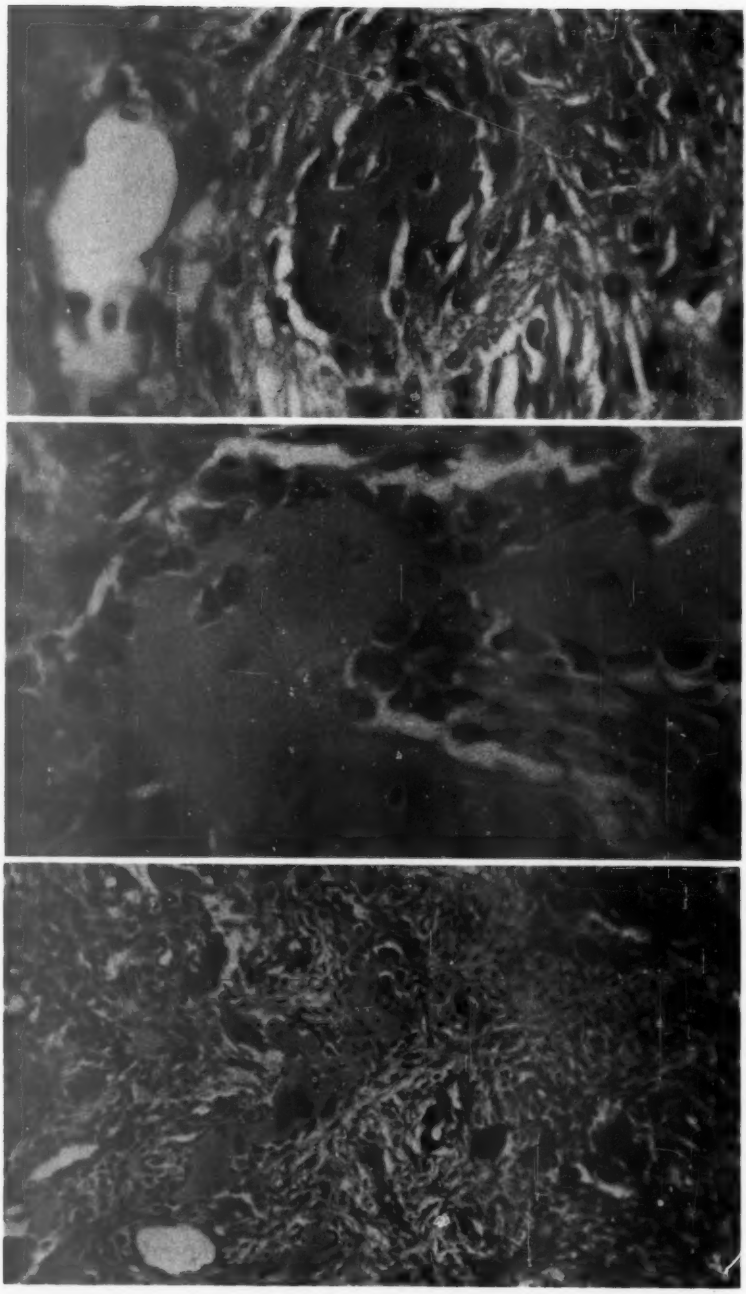
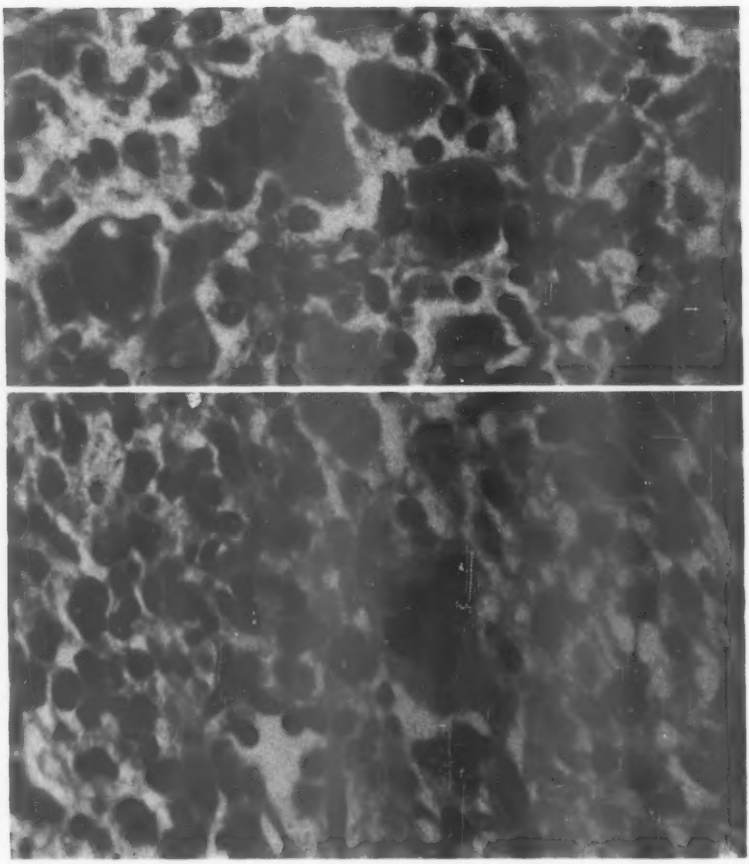


FIG. 4. Grade I giant cell tumor of bone. Well defined multinucleated giant cells with nuclei having the same size, shape, and staining reactions as the nuclei of the mononuclear tumor cells. × 360.

FIG. 5. Grade II giant cell tumor of bone. Giant cell formation not as well defined as in Figure 4. Nuclei of the giant cell vary in size and shape, resembling closely the nuclear variations of the mononuclear cells. × 360.

FIG. 6. Grade III giant cell tumor of bone. Giant cell formation less well defined than in Figure 5. Large bizarre nuclei in giant cell surrounded by mononuclear cells containing the same malignant-appearing nuclei. × 360.

FIG. 7. A small group of multinucleated giant cells is shown. Fusion of the cytoplasm of some of the mononuclear cells with the cytoplasm of the giant cells can be seen. × 600.



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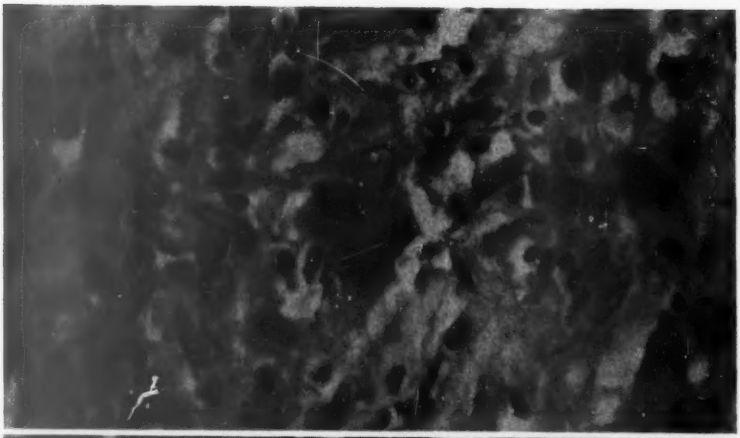

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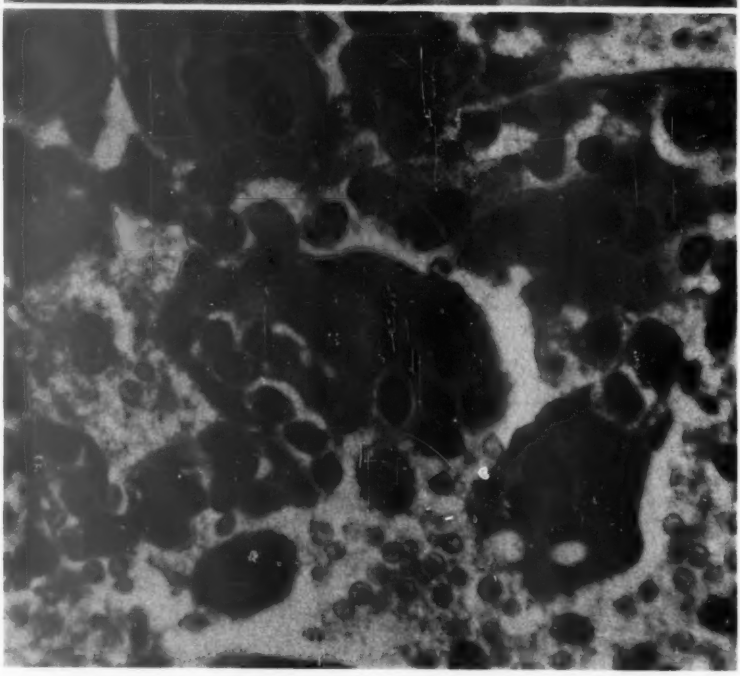

STUDIES ON HAMARTOMAS

I. Cavernous Hemangioma of the Epicardium *

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A cavernous hemangioma is a spongy mass of wide blood-filled spaces which are pleomorphic in shape and dimensions. In contrast to other wide-channeled hemangiomas, the walls of the constituent vascular units are not individualized but are partitions shared in common by adjacent vascular spaces. The intercavernous septa are mesenchymal and predominantly fibroblastic. Collagen deposition varies and often stains atypically. Smooth muscle cells and elastic fibrils may be observed.

The following report deals with cavernous hemangiomas of the epicardium. These lesions usually do not exhibit clinical symptoms referable to the mediastinum or the pericardial sac, such as are described[1] for some other tumors of the epicardium. Consistency, rate of growth, location, and topographic relationship may account for this difference.

Review of the Literature

Five acceptable cases of cavernous hemangioma of the epicardium reported in the literature[2-6] are summarized in Table I. The present case is thus the sixth recorded instance.

The lesions were usually discovered as incidental necropsy findings on the anterior surface of the heart of males of the sixth or seventh decades. In the present case, as in two others,[2,3] they were located on the right side of the heart.

Grossly, the tumors were quite similar, presenting as blue, elevated masses smoothly covered by epicardium. Their surface contours were convex. They varied considerably in size, from 1.0 by 1.0 by 0.5 cm.[4] upward, but all others were smaller than the one to be described, which measured 10.0 by 7.7 by 5.5 cm. With the exception of Koch's case,[5] they were broad-based. They had a spongy structure. Koch noted that the size of the caverns diminished from the center outward, and we observed a similar picture. Organized blood clots were encountered in three or four cases.[2-5] None had produced hemopericardium.

Only one case[3] was documented by photomicrography although all

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had microscopic descriptions. The tumors were well delineated against the underlying myocardium and in some places appeared encapsulated; yet, they were insinuated between epicardial fat cells and in several instances between myocardial fibers.[3,6] The intercavernous septa were collagenized and contained a variable number of spindle-shaped cells as well as focal collections of small and large round cells. Elastic fibrils and smooth muscle cells were described in varying proportions. Leichtweiss[2] was impressed by the unpredictable quantitative relation between fibrous, muscular, and elastic components in the intercavernous septa. He stated that the elastic elements never formed any closed rings but rather showed more or less frequent and more or less conspicuous interruption of continuity. We noted the same pattern.

Exceptional is the case documented by Hochberg and Robinson[5] in that not only was the patient a female and a child (8 years old) but also the cavernoma caused symptoms and was demonstrable roentgenologically. Surgical removal of the tumor resulted in cure.

Thus it appears that cavernous hemangiomas of the epicardium do not rupture or cause external hemorrhagic leakage such as may occur with other types of hemangioma.

The lesions reported by Lefas,[7] Bencini,[8] Pommer,[9] and Timme[11] are not acceptable cavernous hemangiomas of the epicardium. Lefas' case was an angioma simplex of the epicardium. It caused acute cardiac tamponade in a 76-year-old woman. The lesion was approximately 5 cm. in diameter. Case 1 of Bencini[8] is rejected for a similar reason. In an 18-day-old male infant, hemopericardium resulted from rupture of a telangiectatic *capillary* hemangioma located upon the anterior left ventricle near the root of the pulmonary artery.

The case of Pommer[9] of a 51-year-old woman dead from malignant melanoma is difficult to evaluate. Originally reported as "angio-fibro-leiomyoma teleangiectaticum et cavernosum calcificatum et ossificatum haematodes" of the epicardium, it was subsequently reclassified by the author as cavernous hemangioma.[10] The lesion was huge, indeed larger than the heart itself. It overlay the right side of the heart displacing the right atrium superiorly and posteriorly.

The case of Timme[11] was a cavernous hemangioma but was omitted because of its location on the anterior parietal pericardium rather than on the epicardium. This tumor, 2.5 cm. in diameter, was found incidentally at necropsy in a 58-year-old woman dead from congestive heart failure.

Report of Case

D. F. (B.I.H. M22185), a 61-year-old man, had suffered an acute myocardial infarct 19 years previously. Subsequently, he had experienced rare attacks of angina pectoris. The patient continued working as a door to door canvasser.

Three weeks prior to admission he had been awakened from sleep by transient but severe chest pain. An electrocardiogram then showed normal sinus rhythm and myocardial ischemia in addition to changes indicating an old anteroseptal and posterior infarct. The heart was enlarged to the left anterior axillary line. The cardiac sounds were of good quality and there were no murmurs. Bed rest for 2 weeks was advised.

One week later, just before admission to the hospital, the patient experienced severe chest pain, and went into circulatory collapse. When admitted, the blood pressure was 88/70 mm. of Hg. The heart rate was rapid and the rhythm regular. There was an apical systolic gallop and a grade III apical systolic murmur. The sounds were of poor quality. One hour later the patient died suddenly.

Necropsy (A 51-96) revealed pulmonary edema, a multinodular thyroid gland weighing 47 gm., a pancreatic cyst measuring 1.0 cm. in diameter, several cysts in both kidneys of 0.5 to 2.5 cm. diameter, cholesterolosis of the gallbladder, prostatic hypertrophy, and a solitary adenomatous polyp of the sigmoid colon.

The heart, as viewed *in situ,* was grossly enlarged. There was an apical aneurysm of the left ventricle. Here the wall was partially calcified and adherent to the parietal pericardium by dense fibrous adhesions. Otherwise the pericardial sac was not remarkable. Presenting on the anterior epicardial surface of the right side of the heart and elevated for 1.5 cm., there was a blue, oval mass (Fig. 1) of cystic compressibility. The free surface of this mass was strikingly flattened as though moulded by its impact on the bony chest cage (Fig. 2). It was shiny, smooth, somewhat bosselated, and fully and tautly invested by the epicardium. Its long axis corresponded approximately to the long axis of the heart. Divided roughly by the plane of the atrioventricular groove (Fig. 3), the upper half of the tumor occupied the space between the root of the pulmonary artery and the right auricular appendage, rotating the latter to the right. The lower half of the tumor covered the base of the right ventricle (Fig. 1). The mass measured 10.0 by 7.7 by 5.5 cm. Its greatest thickness (5.5 cm.) was at the level of the aortic valve, more specifically over the right coronary ostium (Fig. 3). Much of the tumor protruded in the direction of the right ventricular cavity and had therefore thinned the anterior wall of the right ventricle, flattening and partially effacing its trabeculae.

The cut surface of the tumor was spongy. Sturdy, though delicate, septa subdivided variously shaped spaces filled with blood and measuring from pinpoint to more than 1.0 cm. in diameter. There was no gross evidence of organized thrombi. The largest caverns were found centrally (Fig. 2).

The heart was injected and unrolled by the method of Schlesinger.[12] Because the right coronary ostium was completely surrounded by tumor and markedly narrowed, it was not cannulated. Radiologic

TABLE I

Summary of Reported Cases of Cavernous Hemangioma of the Epicardium

Author	Age	Sex	Symptoms	Cause of death	Size of tumor	Gross description	Microscopic description	Remarks
Czapek,[8] 1891	56	M	None	Pulmonary emphysema	6 x 6 cm.	Blue mass at the apex of the heart, covered by epicardium	In general, sharply delineated against the myocardium though focally insinuated into it; admixture with epicardial adipose cells peripherally; intercavernous septa composed of fibrillary fibrous tissue, occasionally cellular	
Koch,[5] 1912	51	M	None	Cerebral vascular accident	5 x 3 x 1.5 cm.	Bluish-red, oval, pedunculated mass attached to the left ventricle in the anterior longitudinal sulcus, at the level of the anterior pulmonary valve cusp; covered by epicardium; on cut section largest caverns found centrally; no connections to arteries or veins by probing	Intercavernous septa contained numerous elastic fibers with varying numbers of round and spindle-shaped cells, and small vessels (arteries)	This is the case which is misspelled in Moenckeberg's text [22] as "Hoch"
Leichtweiss,[3] 1913	54	M	None	General paresis, atherosclerosis	Triangular, longest dimension 7.5 cm.	Dark, bluish-red mass occupying the niche between the great vessels and the right auricular appendage; covered by taut epicardium; auricular appendage displaced upward and compressed; mass could not be dissected off the aorta; diffuse pericardial fibrous adhesions	Intercavernous septa composed of hypocellular connective tissue, smooth muscle and elastic fibers; yellow-brown pigment in trabeculae; some central caverns filled with thrombi	
Greenberg and Angrist,[4] 1948	63[23]	M[23]	None	Postoperative peritonitis	1 x 1 x 0.5 cm.	Deep-red mass in the atrioventricular sulcus	Tumor sharply demarcated from surrounding fat tissue; some of the caverns contained thrombi	Cavernous hemangioma of liver and leiomyoma of renal capsule found at necropsy
Hochberg and Robinson,[2] 1950	8	F	Fatigue, dyspnea on exertion	Living	9 x 6 x 3.5 cm.	Mass located on the anterior and posterior aspects of the right side of the heart, extending from the entrance of the superior vena cava to the diaphragm; authors believed the tumor to have originated in the epicardium[24]	Intercavernous septa contained delicate connective tissue, smooth muscle, small round cells, and large mononuclear cells; organized clot present in some caverns	
Reiner and Silberg, 1953	61	M	None	Coronary artery disease	10 x 7.7 x 5.5 cm.	Blue mass over right ventricle, extending upward over the roots of the great vessels; right auricular appendage displaced to the right	Intercavernous septa composed of hypocellular collagen, occasional bundles of smooth muscle cells, and fine elastic fibrils; no proper organization into pattern of normal vessel walls	Pancreatic and renal cysts also found at necropsy

contrast mass was injected only into the left coronary ostium. Nonetheless, the right coronary arterial tree was filled by the collateral circulation, and there was slight leakage of mass from its mouth. There were multiple arteriosclerotic narrowings and occlusions of the left and right coronary arteries and their branches (Fig. 3).

The ostium of the right coronary artery projected almost exactly onto the center of the epicardial mass (Fig. 3). The main artery and several of its branches, atypically arranged, were lifted away from their usual intimacy with the myocardium and ran directly through the tumor (Fig. 2). With the exception of a single delicate twig which seemingly terminated in the tumor, the right coronary artery and its branches, both large and small, merely traversed it on their way to the underlying myocardium. This was judged not only from dissection but also from detailed roentgenograms of tissue slices. No radiopaque mass was extravasated into the tumor stroma nor was any mass found in the cavernous spaces or in the cavities of the right atrium or ventricle. Venous connections to cardiac veins or cardiac cavities could not be found by dissection and probing.

On microscopic examination, the cavernous hemangioma fulfilled the criteria outlined earlier (Fig. 4). The joint walls between the caverns were composed predominantly of hypocellular collagen often staining atypically with trichrome or van Gieson's stains. There were infrequent and discontinuous bundles and nests of smooth muscle cells as well as exceedingly fine elastic fibrils. Neither the smooth muscle nor the elastic elements were arranged to establish organized vessel layers. Rather, these specialized mesenchymal elements were distinctly random in quantity and topographic distribution (Fig. 5).

The septa contained occasional collections of lymphocytes of varying density and size, never fashioned into follicles. These nests were particularly dense and numerous about the periphery, both inside and outside the hemangioma. There were also collections of larger round and elongated cells of uncertain identity. Stained with hematoxylin and eosin, their cytoplasm was smooth and salmon-pink. In some, the nucleoplasm was evenly pyknotic or divided into bi-partite or tripartite marginal clumps (Fig. 6).

The cavernoma was fully clothed on the pericardial surface by the stretched but otherwise intact limiting membrane. On the opposite surface, the tumor was separated from the myocardium by a layer of epicardial adipose tissue (Fig. 7), variably attenuated. In a single microscopic section there was superficial insinuation between myocardial fascicles (Fig. 8). The hemangioma was partially invested by

a fibrous capsule which was interrupted by outcroppings of endothelium-lined blood channels extending between epicardial fat cells and accompanied, or more likely preceded, by tongues of hypocellular fibrous connective tissue (Fig. 9). The smallest channels, thus formed, resembled giant capillaries which, it is probable, subsequently enlarged to cavernous proportions. The cavernoma did not appear to enlarge by incorporation and ectasia of pre-existing capillaries indigenous to the site. Nowhere in the cavernoma was there any evolution of organized wall structure of adult vessel types.

These connective tissue tongues were interpreted as the matrix of the cavernous hemangioma. For a growing tissue, the scant cellularity (Fig. 9) of even the youngest and, as yet, non-vascularized connective tissue was noteworthy. With vascularization and subsequent enlargement of the channels to cavernous dimensions there was only little differentiation in the septa toward mesenchymal derivatives such as smooth muscle and elastic tissue and none toward any fixed pattern. This was true, also, of the collagen about the vascular spaces. These observations were interpreted as establishing the essential identity of the "matrix" at the growing border and the fully developed intercavernous septa (*cf.* Figs. 4 and 9).

Discussion

Mechanical compression of the cavernoma was indicated by the marked flattening of its external surface against the bony chest cage and by attenuation and partial effacement of the trabecular contour in the right ventricle. However, the tumor failed to cause clinical symptoms of diminution of the pericardial cavity (chronic tamponade) or of mechanical encroachment upon the heart. Slowness of growth, compressibility of the cavernoma, and low counter-pressure of the right ventricle may have afforded adaptive compensation. The case of Hochberg and Robinson[8] offers a contrasting example of less chronic cardiac tamponade. Symptoms of only a few months' duration from a large mass, 9 by 6 by 3.5 cm., on the heart of a child probably can be correlated with speedy enlargement of the angioma. We believe that the rate of growth was related to the age of their patient.

Virchow[13] characterized cavernous hemangiomas as formations which, in essence, occupy the position of the normal capillary apparatus in that they are intercalated between feeding arterioles and draining veins. His stress on the circulatory topography of cavernous hemangiomas was derived from a controversy between himself and Rokitansky.[14] The latter held the view that cavernous hemangiomas

are formations originally unconnected with any systemic blood vessels; whatever blood is present in them is first produced within the hemangioma itself by a sort of extramedullary hematopoiesis; vascular connections are established later, and only to neighboring veins by erosive action.

In support of their respective opinions, both observers utilized injection studies. Only Virchow was successful in filling cavernous hemangiomas from the arterial as well as the venous side. In our case the radiopaque mass injected into the coronary arteries did not enter the hemangioma. The results of injection studies depend on a number of variables such as pressure head, fluidity of the blood within the vessels, physical characteristics of the injection mass, and localization of the mass after injection. We injected the coronary arteries at room temperature under a pressure of 200 mm. of Hg with Schlesinger's modified mass,[15] which regularly enters vessels no smaller than 40 μ. Under these conditions delicate arteries (200 μ or larger) traversing the cavernous hemangioma became just visible in the roentgenograms. No massive injection into the cavernoma or leakage into the stroma of the hemangioma was detected in either the roentgenograms or numerous microscopic sections. The blood within the cavernous spaces was liquid at the time of injection. This probably means that the arteries traversing the angioma either did not supply it or that immediate inflow into the cavernous spaces took place from the arterial side by way of channels smaller than 40 μ.

Virchow[13] conceived peripheral enlargement of a cavernoma to be ushered in by some proliferative influence (irritation) on neighboring tissues, which are thus transformed into a matrix for vascular neoformation (granulation). Subsequently, cavernomatous transformation takes place not merely by passive dilatation of the newly formed vessels but also by active hyperplasia of the endothelium and other elements of their walls. True capillaries are not produced. Ribbert[16] also rejected the idea that cavernomas enlarge by incorporation of preexisting vessels. He proposed, however, that the vessel-forming matrix belongs to the hemangioma itself and is not furnished by its neighboring tissues.

Hemangiomas constitute a pathologic entity with various morphologic subgroups such as cavernous, capillary, arterial, and mixed. For all their *prima facie* similarities, the vessels of hemangiomata of any variety deviate in structure, and probably also in function, from their adult counterparts. Thus, cavernous hemangiomas resemble erectile tissue but the latter's proper organization of such mural elements as

smooth muscle and elastic fibrils is totally missing in both kind and arrangement. The lack of closed elastic and muscular rings commented upon by Leichtweiss[2] is not, we believe, a result of tearing from undue distention of the vascular channels, but rather an inherent fault of construction of the cavernous walls and an *a priori* manifestation of its inherent faculties. Similarly, although the smallest endothelium-lined blood channels of the connective tissue tongues at the progressive border of our tumor resembled giant capillaries, they did not appear to function as nutrient vessels for the neighboring tissues nor primarily for the stroma of the hemangioma.

Albrecht[17,18] introduced the concept of hamartoma (hamartanein = to err) and defined it as a localized error in composition of the tissue elements of the host organ. In terms of the architecture of the host organ, this error might express itself in three ways, singly or in combination: by abnormal quantity, by abnormal structure, or by degree of evolution and maturation of one or the other of the tissue components.

Hemangiomas, as a group, are accepted as hamartomas.[19] Yet, and especially for them, Albrecht's definition appears too narrow. Hemangiomas are derived from a ubiquitous matrix and hence lack the organ specificity which is necessarily implied in Albrecht's definition. Moreover, while hemangiomas, and especially the cavernous variety, are characterized by erroneous structure, the abnormality is not in relation to any special characteristics of the vessels of the host organ but rather to the principles of vessel construction in general. Finally, the error is not representative of arrested development of angiogenesis of host tissue, but is an aberrant or dysplastic development. Nonetheless, hemangiomas possess considerable capacity for mimicry of normal adult vessel types. This may materialize over a considerable range of aberration, both in terms of vessel size and vessel type, and also of biologic behavior from restraint to aggressiveness of growth. Probably the morphologic type of a given hemangioma is not determined by the mechanical conditions of intravascular blood pressure, as Benda[20] proposed for the cavernoma. More likely, the morphology of the hemangioma—cavernous, arterial, capillary, or mixed—is determined essentially by its matrix. We may retain the term hamartoma to designate a broad group of lesions intermediate between dysplasia and neoplasia (neodysplasia[21]). These may be errors not only of organ construction in Albrecht's sense, but also of tissue construction, or of both.

The "incidental" findings of cavernous hemangioma of the liver and leiomyoma of the renal capsule in the case of Greenberg and Angrist[4]

and the pancreatic and renal cysts in our case are interpreted as manifestations of a hamartomatous complex.

Summary

The sixth case of cavernous hemangioma of the epicardium (visceral pericardium) is reported. Cavernous hemangiomas in this location are usually asymptomatic and found incidentally at necropsy in males in the sixth or seventh decades. They are not prone to external hemorrhage. Injection of the coronary artery did not fill the cavernoma.

The assignment of cavernous hemangioma to the class of hamartoma is accepted, but modified. Cavernous hemangioma, like any other hemangioma, is not a localized error of composition of tissue elements of its host organ but, in whatever organ found, expresses an error of blood vessel construction.

Dr. Monroe J. Schlesinger offered suggestions and criticism in the preparation of the manuscript. Dr. David Ayman supplied some of the clinical data.

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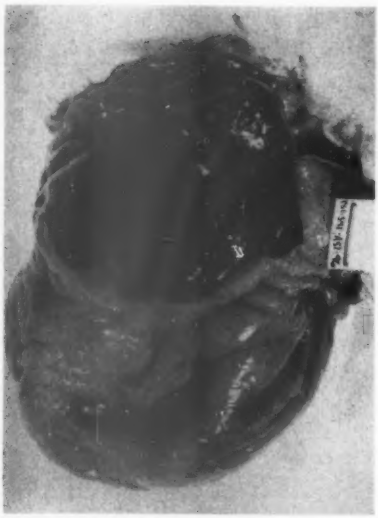
LEGENDS FOR FIGURES

FIG. 1. Anterior aspect of the heart. The upper half of the cavernous hemangioma of the epicardium occupies the space between the root of the pulmonary artery (upon which lies the label) and the right auricular appendage. The lower half covers the base of the anterior right ventricle. The long axis of the angioma corresponds roughly to the long axis of the heart. The collapsed wall at the apex of the left ventricle is a cardiac aneurysm.

FIG. 2. Cross section of cavernous hemangioma of the epicardium. The outer surface (top, in the photograph) facing the chest wall is flattened. The mass protrudes in the direction of the right ventricular cavity. The cavernoma has a spongy makeup. The largest caverns are central. The irregular white dot (arrow) is a radiopaque mass in the right coronary artery.

FIG. 3. Roentgenogram of the heart, injected and unrolled by the method of Schlesinger.[12] Only the ostium of the left coronary artery could be cannulated. Nevertheless, the entire coronary arterial tree was filled with radiopaque mass. A bit of mass has leaked from the ostium of the right coronary artery into the sinus of Valsalva. The aneurysm of the left ventricle is on the left in the photograph. The cavernous hemangioma is the oval shadow on the right. It is roughly halved by the atrioventricular groove; onto its center projects the ostium of the right coronary artery.



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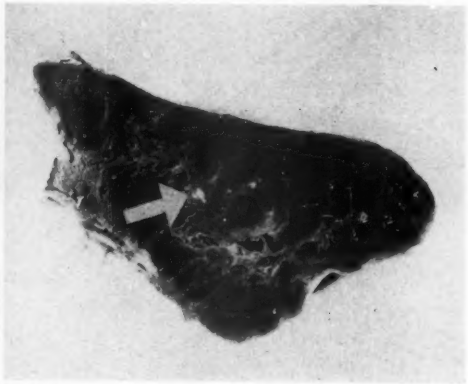

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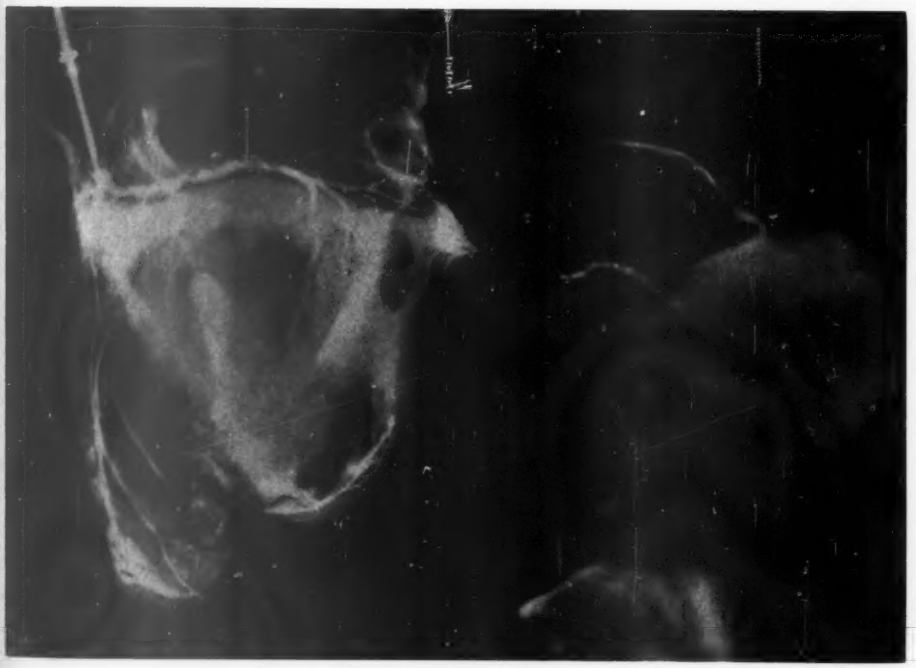

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FIG. 4. Cavernous hemangioma of the epicardium. The intercavernous septa are sturdy partitions shared in common by adjacent vascular spaces. Hematoxylin and eosin stain. × 28.

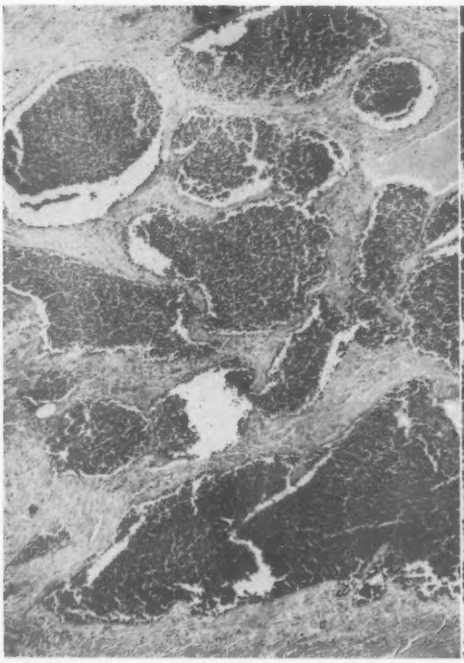
FIG. 5. Cavernous hemangioma of the epicardium. Smooth muscle bundles are without pattern. Trichrome stain. × 88.

FIG. 6. Cavernous hemangioma of the epicardium showing a collection of smoothly contoured, round and elongated cells. Some of the nuclei present bipartite or tripartite marginal clumping. The hollow space at the right of the photograph is an epicardial fat cell. Hematoxylin and eosin stain. × 480.

FIG. 7. The inferior border of the cavernous hemangioma of the epicardium (top of photograph) is a straight line in this section. A substantial layer of somewhat compressed epicardial fat intervenes between the hemangioma and the myocardium. A twig of the right coronary artery is in the upper left. Van Gieson's stain. Low power.

FIG. 8. Cavernous hemangioma of the epicardium insinuating itself into the superficial myocardium. Trichrome stain. × 84.

FIG. 9. Advancing border of the cavernous hemangioma of the epicardium. Of note are the hypocellular collagen between the epicardial fat cells and the vascularization by endothelium-lined blood channels. Hematoxylin and eosin stain. × 84.



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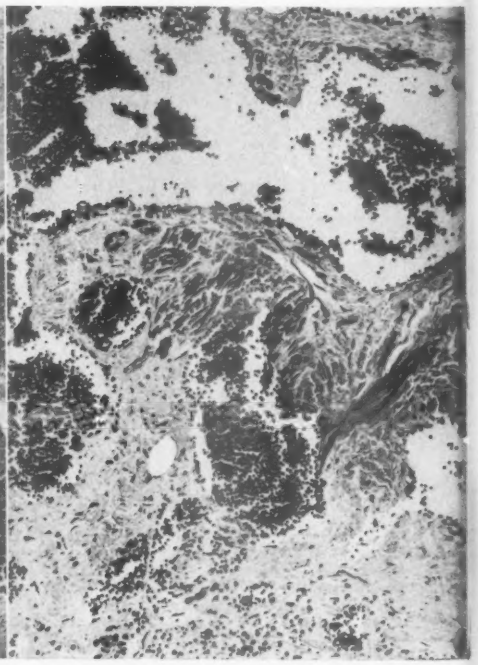

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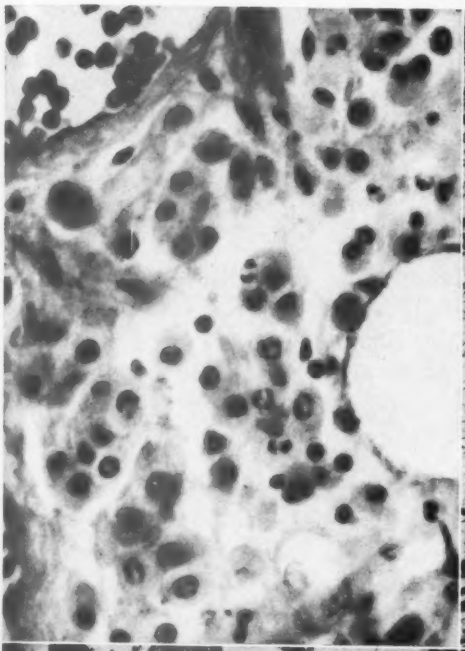

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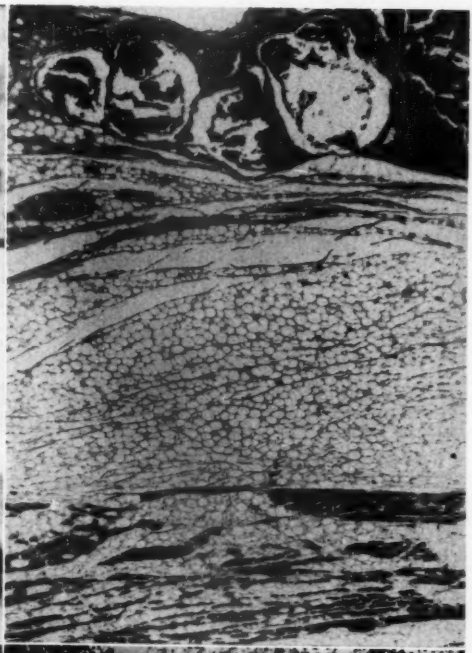

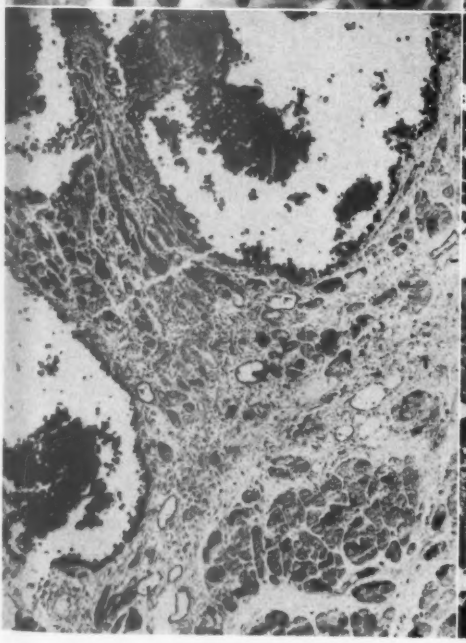

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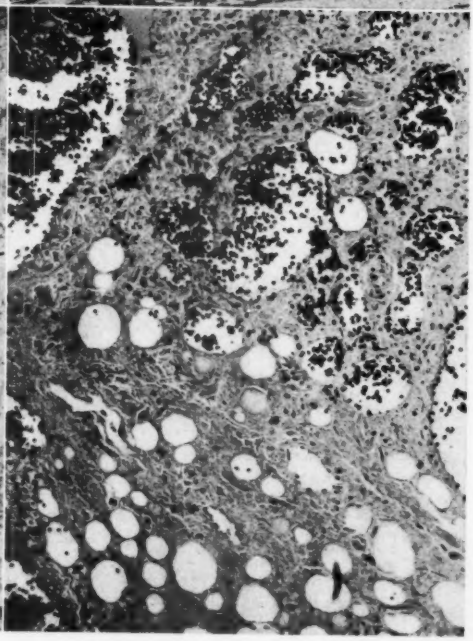

9

SIMILARITIES BETWEEN THE LESIONS IN HUMAN MALIGNANT HYPERTENSION AND IN THE HYPERTENSIVE STATE OF THE NEPHRECTOMIZED DOG *

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The description by Fahr,[1] and subsequent considerations such as discussion by Klemperer and Otani,[2] have established arteriolar necrosis, particularly within the kidney, as the outstanding vascular lesion of human malignant hypertension. It has been demonstrated repeatedly[3-8] that bilateral nephrectomy of the dog is followed in time by arteriolar lesions in various viscera that resemble closely, when studied by routine stains, the arteriolar lesions of human malignant hypertension. Moreover, bilateral nephrectomy of the dog may be associated with the development of a pronounced and sustained hypertension[9-11] which has the hemodynamic characteristics of human malignant hypertension.[12] In view of the hemodynamic and morphologic similarities between the human disease and this special experimental preparation, it appeared worth while to investigate the two lesions further by means of a series of histochemical procedures. The present communication relates the result of such a study. It is appreciated that morphologic similarities do not necessarily link the canine and human lesions in a causal way.

METHODS

The tissues studied were obtained fresh and frozen, then fixed in suitable fixatives for the histochemical procedure employed. The human tissues were taken from kidneys obtained at necropsy from patients dying of clinically and morphologically demonstrated malignant hypertension. The canine tissues studied were taken from the large bowel of dogs subjected to bilateral nephrectomy and then kept alive by peritoneal dialyses until hypertension and the accompanying arteriolar lesions developed. The histochemical techniques are described in the standard works on histochemistry.[13,14] Minor changes in methods will be mentioned.

The lipid components of the lesions were studied by the following staining procedures: oil red O, Nile blue sulfate, Schultz's, Sudan black

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B, osmic acid, and Baker's acid hematin reaction with pyridine extraction as a control. The aldehyde groups were demonstrated by the Schiff reaction on frozen sections of formalin-fixed material. Sulfuric acid esters of polysaccharides were stained by the Congo red amyloid stain using frozen sections of formalin-fixed tissue. Mucin was stained by Best's mucicarmine method. Glycogen was stained by Best's glycogen stain. Alkaline and acid phosphatase were demonstrated by the method of Gomori. Free carbonyl groups were demonstrated by the method of Ashbel-Seligman.[15] Potassium was demonstrated by Macallum's method as modified by Gomori.[13] Protein bound sulfhydryl groups were demonstrated by the method of Barrnett and Seligman.[16]

Results and Comments

The various histochemical procedures used yielded results indicating no differences in the staining characteristics of the arteriolar lesions of the human kidney in malignant hypertension and the arteriolar lesions of the dog following bilateral nephrectomy. The lesions studied were representative of necrotic arterioles from the human kidney and from the large bowel of the dog. This is the classical lesion of malignant hypertension, being considered to result mainly from an acute medial necrosis of the arteriole. The entire wall is represented by an intensely eosinophilic mass in which none of the normal architecture appears to exist.

This lesion contains various substances as evidenced by these positive histochemical tests. Triglycerides and fatty acids were demonstrated by a positive oil red O (Fig. 1) and Nile blue sulfate stain. The fact that the predominent color in the Nile blue sulfate stain was blue seemed to indicate that the majority of the lipids were present as acidic lipids. Cholesterol was present as a part of the lipid component as evidenced by the positive Schultz reaction. This test is not completely specific for cholesterol; however, it appears that cholesterol and its esters account for the major portion of the color reaction.[18] The other lipid stains were Sudan black B, osmic acid, and Baker's acid hematin reaction; these were negative. These stains have been considered to be positive in the presence of phosphatides, triolein and oleic acids, and phospholipids respectively. The Schiff's reaction (Fig. 3) on the frozen section of the formalin-fixed tissue was positive, indicating that free aldehyde groups were present. The fact that this reaction was more strongly positive when frozen tissue was employed than when paraffin-embedded tissue was used, suggested that part of the material consisted of aldehyde groups associated with carbohydrates, and part as aldehyde groups associated with lipid aldehydes;

presumably a small fraction of the positive reaction resulted from the reaction of aldehyde groups associated with elastic tissue. Alcohol or acid extraction failed to modify the reaction. The positive Congo red amyloid stain on frozen section indicated the presence of sulfuric acid esters of a polysaccharide, thus offering confirmatory evidence of the presence in the lesions of polysaccharide complexes. Free carbonyl groups were present (Fig. 2), as demonstrated by the Ashbel-Seligman technic.[15] Potassium was present (Fig. 4) in the lesions as demonstrated by Gomori's modification of Macallum's method.[18] Protein-bound sulfhydryl groups were demonstrated by a positive reaction utilizing the method of Barrnett and Seligman.[16] Acid phosphatase was demonstrated (Fig. 5) by a positive reaction using Gomori's method.[18] The lesions were found to contain neither mucin, as shown by Best's mucicarmine stain; nor glycogen, by Best's glycogen stain; nor alkaline phosphatase, by Gomori's method; nor nonspecific esterase, by the Nachlas and Seligman[17] method.

These histochemical procedures are not considered to be quantitative. It would appear, however, that the necrotic lesions give more intense reactions with the following procedures than do normal arterioles or normal smooth muscle: oil red O, Nile blue sulfate, Schultz's reaction, Schiff's reaction, Congo red, acid phosphatase, and potassium. They appear to give the same reactions for the free carbonyl groups and protein-bound sulfhydryl groups as normal arterioles, and normal smooth muscle.

All of the substances mentioned are present in normal smooth muscle to some extent. Their apparent increment following injury of the arteriole may be simply a result of an alteration in their physiochemical state due to the necrosis of the media, rather than of an actual increase in their amount. Thus, one does not have to assume that these materials enter the wall of the arteriole from the blood stream; and the eosinophilic material of these lesions can be accounted for more plausibly on an intrinsic than on an extrinsic basis.

Summary

The acute arteriolar lesions occurring in humans with malignant hypertension and in dogs following bilateral nephrectomy have been subjected to a variety of histochemical procedures. Similar results were obtained in the vascular lesions from these two sources.

The lesions appear to result fundamentally from necrosis of the media of the arterioles.

The lesions contain lipids, carbohydrates, free carbonyl groups, protein-bound sulfhydryl groups, free potassium, and acidic phosphatase.

All of the histochemically identifiable materials are found in normal smooth muscle; thus it is probable that the compounds identified by the histochemical methods are derived from the muscle.

An apparent increase in the reactions of some of these procedures, *i.e.*, oil red O, Nile blue sulfate, Schiff's reaction, Schultz's reaction, Congo red, potassium, and acid phosphatase, is considered more likely to result from an unmasking of the substances as a result of physiochemical changes following necrosis (an intrinsic source).

We wish to acknowledge the technical assistance of Ovia Walker.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. Arteriole in canine bowel, stained with oil red o.

FIG. 2. Arteriole in canine bowel. Free carbonyl reaction of Ashbel and Seligman.

FIG. 3. Arteriole in canine bowel. Schiff's reaction.

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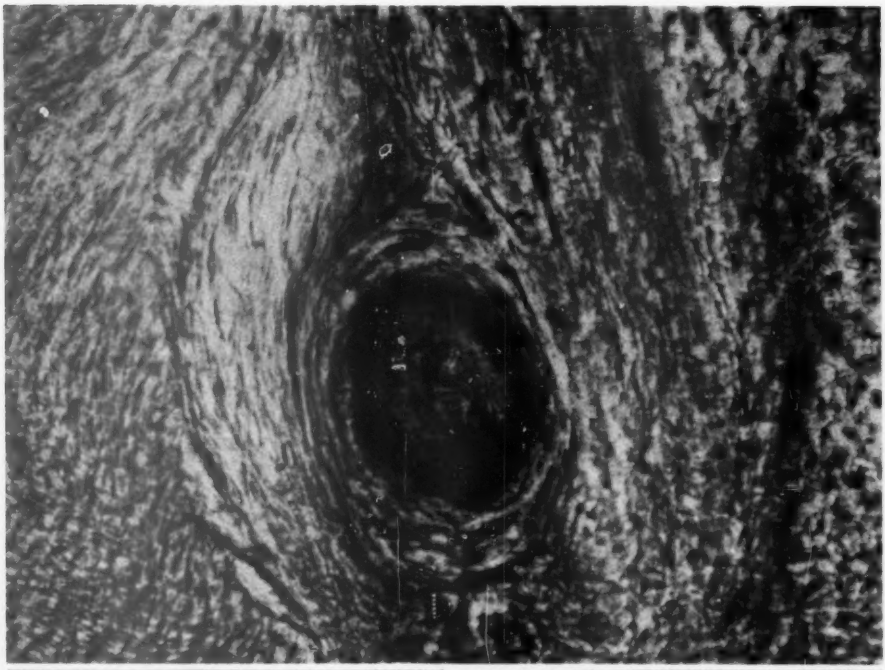

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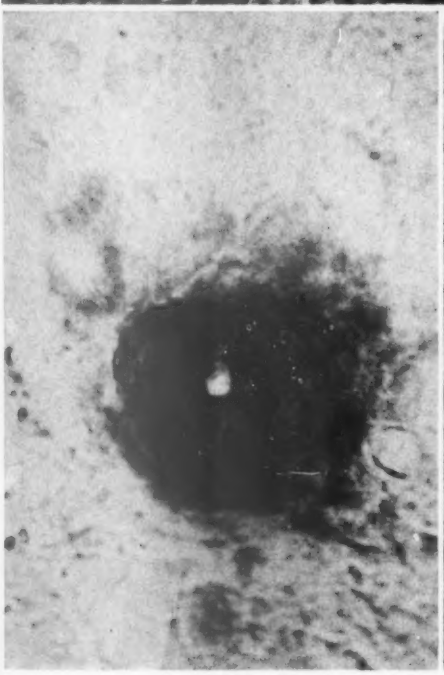

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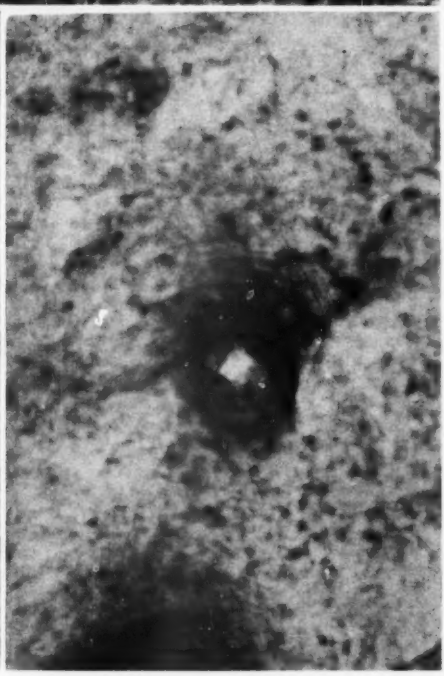

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FIG. 4. Arteriole in canine bowel. Free potassium.

FIG. 5. Arteriole in canine bowel. Acid phosphatase by Gomori's method.

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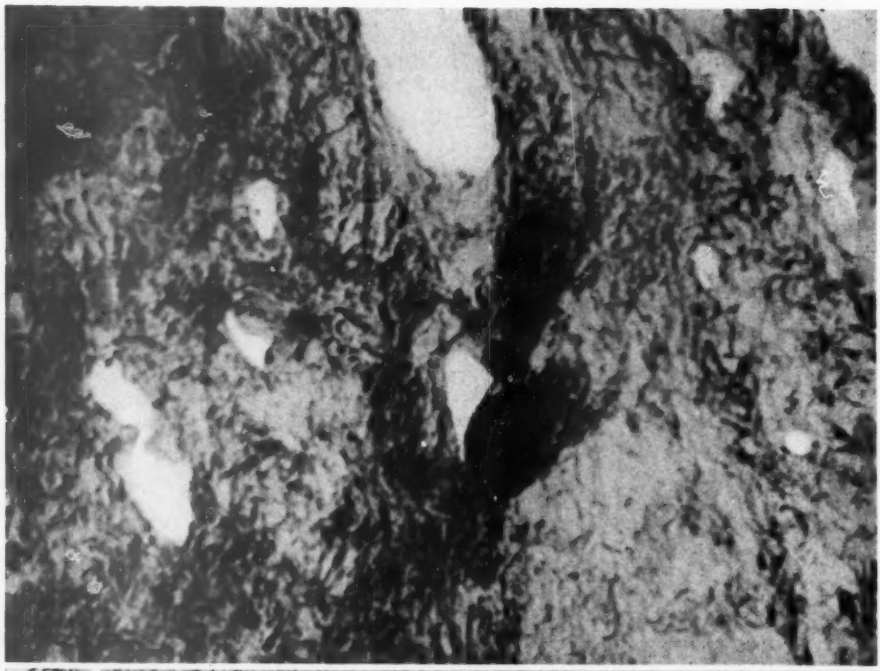

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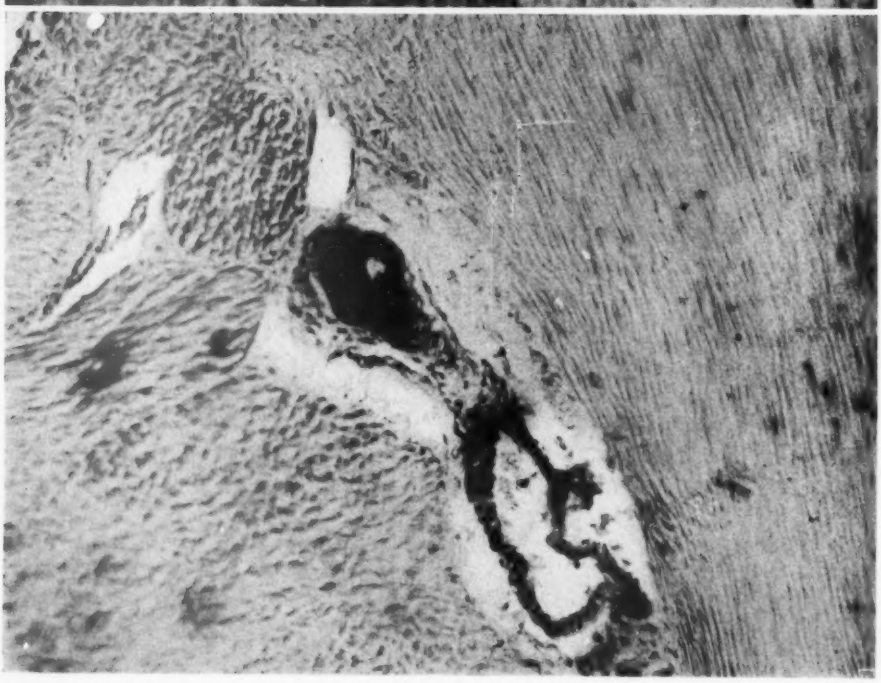

5

ELECTRON MICROSCOPY OF YELLOW FEVER VIRUS (17D STRAIN)*

REGINALD L. REAGAN, Maj. Ret. U.S.A., and A. L. BRUECKNER, V.M.D.
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The 17D strain of yellow fever virus used for this study was furnished by the American Type Culture Collection of Washington, D.C. This virus had originally been obtained from Dr. Sawyer of the Rockefeller Foundation Laboratories. The 229th passage of the 17D strain was received at the Rocky Mountain Laboratory from the Rockefeller Foundation as Lot 145-3 AB 769. The strain has been through 5 passages in embryonated eggs at the Rocky Mountain Laboratory. The 17D strain is widely used for immunization of man against yellow fever. It produces no known visceral lesions in man or monkey when inoculated subcutaneously, but induces a mild systemic disease with small amounts of circulating virus.[1]

MATERIALS AND METHODS

The virus was received here in lyophilized chick embryo tissue and was diluted to a 10 per cent suspension with physiologic saline solution. Twenty Swiss albino mice (3 weeks old) were inoculated intracerebrally with 0.03 ml. of this virus suspension of the 5th egg embryo passage. The mice showed nervous symptoms of involuntary motor reactions and paralysis on the seventh day. When symptoms appeared, the mice were sacrificed and the brains and cords were removed aseptically. Twenty mice were injected intracerebrally with a 10 per cent suspension of normal chick embryo tissue. No symptoms were noted in these normal controls and they were sacrificed on the seventh day after inoculation. The brains and cords were removed aseptically as before. The pools of virus-infected mouse brains and cords and of normal mouse brains and cords were ground with alundum and diluted to 10 per cent suspensions with physiologic saline solution. The two suspensions were then subjected to centrifugation in an angle centrifuge at 2000 r.p.m. for 5 minutes. The supernatants were removed from the specimens and filtered through type ST, size L_3, Seitz filters. The filtrates were then subjected to centrifugation for 3 hours at 44,770 r.p.m. under refrigeration. The temperature of the refrigerated outer jacket stayed constant at –8° C. during the centrifugation. After the 3-hour centrifugation period, the supernatants from the specimens

* Received for publication, May 7, 1953.

were discarded and the sediment from each specimen was resuspended in 0.8 cc. of sterile double-distilled water. Several drops of each suspension were placed on several parlodion film supports which had been prepared 6 days previously. After all excess fluid had been removed with small capillary pipettes, the films were dried and shadowed with chromium[2] at arc tangent 2/10 and examined under the R.C.A. electron microscope, type E.M.U.

The balance of the material of each suspension was injected intracerebrally into 6 Swiss albino mice, 3 weeks old. The mice injected with the concentrated infected material showed paralysis after a period of 7 days. These mice were sacrificed and the brains were removed aseptically, pooled, ground, and diluted to a 10 per cent suspension. A serum neutralization test was conducted with this suspension with specific yellow fever antiserum* and normal human serum, using mice inoculated intracerebrally as the test host. Specific immune serums completely neutralized the virus, while normal human serum did not. This confirmed the concentrated virus to be yellow fever virus. The mice injected intracerebrally with the concentrated suspension of normal mouse brains and cords appeared normal and were discarded after an observation period of 21 days.

Upon electron microscopic examination of the concentrated suspensions of the brains and cords of the normal mice, no virus-like particles could be seen. These controls were screened carefully. Upon examination of the concentrated suspension from the infected brains and cords, uniform virus-like particles were demonstrated as shown in Figure 1. These bodies measured 50 to 55 mμ by direct measurement and were round with a slightly irregular contour.

Summary

Studies by electron microscope of brains and spinal cords of mice infected with yellow fever virus, 17D strain, showed the virus to be round with a slightly irregular contour and with a diameter of 50 to 55 mμ. These bodies could not be demonstrated in concentrated normal mice brains and spinal cords subjected to the same procedure of concentration and examination. These bodies resemble the virus of measles (Morbilli) described by us.[3] By ultracentrifugation studies with yellow fever virus, on the assumption that the virus particle is spherical, the diameter was estimated to be between 12 and 19 mμ.[4] By electron microscopy the 17D yellow fever virus strain is somewhat

* Human yellow fever antiserum was supplied by Dr. Max Theiler of the Rockefeller Foundation. It had been secured by phlebotomy from Dr. Theiler.

larger, probably due to the virus having been carried many passages in tissue culture and many passages in chick embryos.

The virus in the concentrated material was neutralized by specific yellow fever antiserum, while normal human serum had no effect on this concentrated material.

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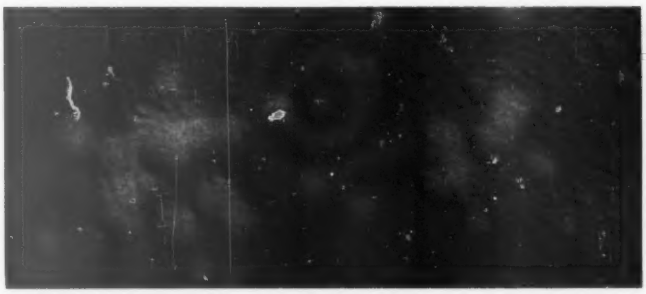
LEGEND FOR FIGURE

FIG. 1. Yellow fever virus shadowed with chromium at arc tangent 2/10. × 110,000.



1

ELECTRON MICROSCOPIC STUDIES OF ERYTHROCYTES FROM A PATIENT WITH INFECTIOUS MONONUCLEOSIS *

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The causal agent of infectious mononucleosis is not definitely known, although a virus is suspected.[1] Electron microscopic studies were conducted to search for virus-like particles in or on the erythrocytes.

Clinical Abstract

A white male, 21 years old, was admitted to Walter Reed Army Hospital on April 22, 1953, complaining of anorexia, nausea, vomiting, and diarrhea for 3 days. On the day after admission the patient had low grade fever and was found to have developed a generalized lymphadenopathy, including rather marked enlargement of anterior and posterior cervical, axillary, submental, and inguinal nodes. Heterophile antibody test on the second day was reported as positive at 1:896. The acute course persisted for 3 weeks. The heterophile antibody titer remained at 1:896 during the 3-week period. The patient was eventually discharged with the diagnosis of infectious mononucleosis.

MATERIALS AND METHODS

Ten cc. portions of venous blood were collected from the patient and placed in sterile 50 cc. Erlenmeyer flasks which contained 14 mg. of heparin in 6 cc. of sterile H_2O. Ten cc. of venous blood was drawn likewise from a patient with no history of having this disease (control). The flasks of infected heparinized blood and the flask of normal heparinized blood were then refrigerated at $-4°$ C. for 2 hours. They were then removed from the ice box and let stand at room temperature for 1 hour, rotating each flask occasionally. Several drops of each suspension were placed on several parlodion film supports which had been prepared 48 hours previously. After all excess fluid had been removed with small capillary pipettes, the films were dried and shadowed with chromium[2] at arc tangent 2/12 and examined under the R.C.A. electron microscope, type E.M.U.

RESULTS

Upon examination of the specimen under the electron microscope, no virus-like particles were observed in erythrocytes from the normal control preparations in approximately 2,000 fields examined. Upon

* Received for publication, June 30, 1953.

electron microscopic examination of the infected blood, uniform virus-like particles were observed. They were present in about 2 per cent of the 2,000 microscopic fields examined. Figures 1 and 2 are electron micrographs showing these virus-like particles on the surface of erythrocytes. The majority of these particles were spherical and measured 160 to 200 mμ by direct measurement. Irregular contours were seen on some particles. This irregularity may be due to the hypertonicity of the suspending fluid during the drying process.

Summary

Electron microscopy of erythrocytes from a patient infected with infectious mononucleosis showed the virus-like particles to be spherical, with irregular contour. The virus-like particles have a diameter of 160 to 200 mμ. These bodies could not be demonstrated in normal human blood subjected to the same procedure of preparation and electron microscopic examination. These bodies resemble the virus of influenza described by Stanley[8] and the virus of measles described by us.[4]

The patient's serum contained heterophile antibodies and other signs were present that are considered diagnostic for infectious mononucleosis.

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FIG. 1. Electron micrograph of an erythrocyte showing virus-like particles on the surface and one virus-like particle outside of the cell. Shadowed with chromium at arc tangent 2/12. × 22,000.

FIG. 2. Electron micrograph of an erythrocyte showing one virus-like particle on the surface of the cell. Shadowed with chromium at arc tangent 2/12. × 22,000.

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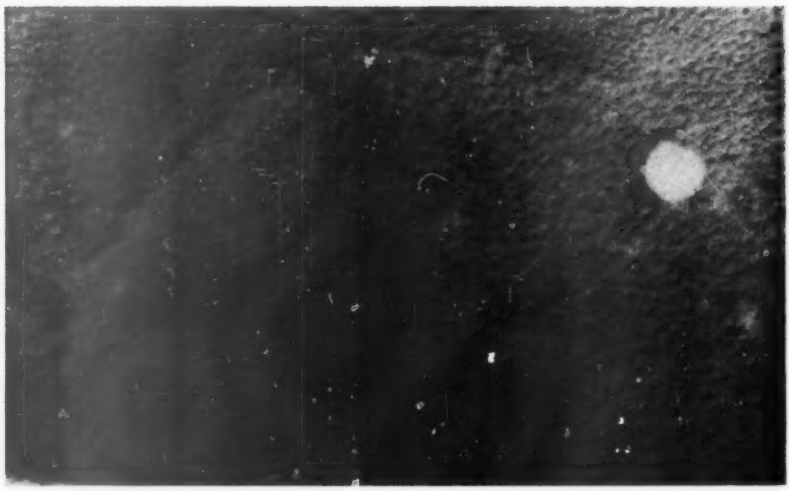

MENINGO-ENCEPHALITIS IN PIGEONS *

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This report concerns an outbreak of disease in pigeons characterized by nervous symptoms, which occurred on a large squab farm on Long Island between June 23 and September 15, 1952. The condition affected 116 of 14,000 breeding birds, but did not affect the approximately 40,000 squabs that were raised on the farm during the outbreak. It ran an apparently self-limited course which was not affected by attempted medication of sick birds. Various birds were treated by intramuscular injection of penicillin, streptomycin, aureomycin, or thiamine chloride. None of these agents altered the symptoms in affected birds, except streptomycin. This antibiotic was fatal within a few hours in a dose of 0.1 gm. per bird. The owner kept about 30 Muscovy ducks in the pigeon pens (as a mouse control measure). These remained healthy during the outbreak.

Clinical Course

The disease was enzootic rather than epizootic in its course. One to 12 birds would be found affected one day, followed by an additional small number a few days later. Torticollis was a prominent symptom, the birds squatting on their hocks with the neck twisted. When disturbed in this position, or if picked up and held, they would rotate the head repeatedly through a 360° circle while the neck remained twisted (Fig. 1). Palpation of the neck revealed spasticity of the muscles.

The muscles of the wings and legs appeared to have normal tonus and neither spasticity nor flaccidity could be detected upon palpation and passive flexion. However, neither the wings nor legs could be coordinated properly. There was ataxia of both flight and walking in affected birds that were not too weak to move. The ataxic movements were studied from motion pictures taken at ordinary speed and projected in slow motion. Although some of the birds were capable of flight, the unequal effort of the wings resulted in a list to one side or the other which would cause them to fall to the ground shortly after take-off. Other birds moved both wings with apparently equal force,

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but misdirected effort, so that the birds flew backwards. Walking, when it could be accomplished, was done in a staggering manner, the birds extending one wing or the other in an effort to maintain equilibrium. After a few days of such symptoms the birds could no longer sit up and would lie on one side with the neck twisted. The pupillary and ocular preservation reflexes did not appear to be disturbed and we detected no nystagmus.

Affected birds retained their appetite somewhat, but, of course, were unable to reach their food. The owner found that he could keep some of them alive by hand feeding. Only one of the hand-fed birds showed eventual remission of the symptoms. If not hand fed, the birds would die in about 4 to 5 days.

Pathologic Findings

Fifteen birds were killed for necropsy, by injecting air into the heart. The only gross change was that of emaciation in birds that had shown symptoms for more than 3 or 4 days.

No pathogenic bacteria were isolated from the brain or blood stream. Blood serum was obtained from 3 pigeons that had been kept alive for 2 weeks by hand feeding. Serum neutralization and hemagglutination-inhibition tests were run against Newcastle disease virus with negative results. Pools of brain and splenic tissue from several affected pigeons were sent to Dr. J. Fabricant at the New York State Veterinary College. He inoculated embryonated chicken eggs with this material and reported that it had no effect on the embryos, and that no virus was isolated after serial blind passages in embryonated eggs. Facilities were not available to us for pigeon inoculation experiments.

Histologic lesions were restricted to the brain, which was subjected to detailed study in 7 birds. The brains were fixed in aqueous formalin. Sections were stained with hematoxylin and eosin, and by myelin sheath and Nissl techniques. These sections were compared with those of 2 normal pigeon brains. One spinal cord from an affected pigeon was compared with one from a healthy bird. The lesions were similar in all of the brains and varied only in extent. The leptomeninges were greatly distended by fibrinous exudate (Fig. 2). This was equally well marked over the forebrain and over the cerebellum and brain stem. In some areas the exudate was almost acellular, whereas in others there were clumps of inflammatory cells, mostly mononuclear. The choroid plexus was distended with fibrinous exudate.

Areas of perivascular cuffing and myelin degeneration were present,

the most severe lesions being in the medulla oblongata and midbrain (Fig. 3). In this region the tissue adjacent to the ventricular system was more severely affected than the peripheral tissue. The general appearance was that of acute non-suppurative encephalitis with necrosis accompanying the exudative phenomena. Myelin destruction occurred in diffuse patches which were not restricted to the boundaries of tracts. Both pyknotic and swollen neurons were present in these areas. Portions of the vestibular and fastigial nuclei were included in affected areas in 4 brains. The evidences of encephalitis did not extend very far either into the forebrain or into the caudal end of the medulla oblongata. Many of the neurons in the Purkinje cell layer of the cerebellum were pyknotic; these were distributed at random between normal-appearing neurons (Fig. 5). No lesions were seen in the other layers of the cerebellum. The one spinal cord that was examined appeared normal.

During the course of this study a report appeared on the presence of Toxoplasma in pigeons captured on the roof of the Capitol in Washington.[1] Our sections were examined with this information in mind, but no Toxoplasma bodies were found. No inclusion bodies were seen in either the neurons or the glial cells.

Discussion

It is not possible to differentiate this syndrome clinically from some other diseases that have been described in pigeons. Similar symptoms have been observed in pigeons with hereditary ataxia, and with supposed thiamine deficiency. In hereditary ataxia, many of the birds are affected when quite young, and the cerebellum shows grossly visible hypoplasia.[1a] The histologic lesions in the central nervous system are degenerative. Since the lesions in our birds were primarily inflammatory, hereditary ataxia can be ruled out on the basis of dissimilar morphologic features.

Pigeons with experimental thiamine deficiency have been reported to show some of the symptoms seen in our birds.[2-4] Follis[5] has recently criticized these experiments, adding his doubts to those of others who do not believe that thiamine deficiency is the cause of the nervous symptoms produced experimentally in pigeons. Without attempting to discuss the merits of either opinion, it is sufficient to point out that the lesions in the experimental disease (whatever its cause) are again degenerative, and are thus distinct from the lesions in our birds. It might be mentioned in passing that the ration of the present flock appeared to be adequate in the known essential nutrients, and the flock

as a whole was in excellent nutritional condition throughout the course of the outbreak. As stated, affected birds did not respond to the administration of thiamine.

In addition to the two diseases mentioned, which differ from that in our pigeons in their morphologic features, the present disease can be distinguished clinically from psittacosis and from I.N.I. virus. Without going into details, our birds showed neither the symptoms, lesions, nor inclusion bodies described in outbreaks of these diseases in pigeons.[6]

Plazikowski[7] described a condition in pigeons which he termed "infectious rotator disease," in which the symptoms were similar to those in our flock. He stated that its anatomical basis was cerebellar meningitis, but gave no details. He considered that it was caused by an infectious agent, but one which had not yet been isolated. Since no details were given about the attempts to establish the cause, we are unable to compare the present condition with infectious rotator disease.

Pallaske[8] described enzootic pigeon paratyphoid, during the course of which a single adult bird developed torticollis. The symptoms were due to purulent meningo-encephalitis, and paratyphoid organisms were isolated from the brain and blood stream. He mentioned that other workers had isolated paratyphoid organisms from the brains of similarly affected pigeons but had been unable to reproduce the symptoms even by intracerebral inoculation. This led them to suspect that some other agent, probably a virus, was present. Paratyphoid can be ruled out in the present outbreak in view of our negative cultural results and the non-suppurative character of the inflammation.

The lesions in the present outbreak were predominantly inflammatory and suggestive of a virus infection. Since the outbreak occurred during the mosquito season, we suspected equine encephalomyelitis, which has been found to occur naturally in pigeons.[9] This virus is pathogenic for chick embryos, and the failure of our material to infect chick embryos would suggest that some virus other than equine encephalomyelitis must have been responsible for the disease, if, indeed, a virus was present at all. We have not found a description of the central nervous system in pigeons affected with equine encephalomyelitis, and hence have been unable to compare the lesions. However, in a natural outbreak of equine encephalomyelitis in pigeons in Massachusetts, the disease was of epizootic proportions and deaths were rapid, differing in these respects from the present disease.

The possibility that avian encephalomyelitic infection was present must be considered since Olitzky[10] stated that young pigeons are susceptible. Since chick embryos are difficult to infect with this virus, this possibility was neither established nor ruled out by our negative isolation results.

The negative serologic tests for Newcastle disease tend to eliminate the possibility of the virus of Newcastle disease being the cause of encephalomyelitis in these pigeons. In a recent account of epizootic Newcastle disease in pigeons, serologic tests were reported positive.[11] The lesions were not described, so that here, too, anatomical comparison is not possible.

No record of a disease of pigeons with similar lesions and similar low incidence and self-limiting properties in the midst of a large flock, has been found in the literature.

Summary

A syndrome characterized by torticollis, ataxia, and eventual prostration was observed as an enzootic disease of 3 months' duration in a large flock of pigeons. The disease was self-limiting, and less than 1 per cent of the flock was affected. Non-suppurative, demyelinating meningo-encephalitis was present in the brains of affected birds. The lesions were suggestive of a viral etiology, but no infectious agent could be isolated or demonstrated histologically and the cause remained undetermined. Comparison of the condition with other nervous diseases of pigeons indicated that this disease entity has not been described previously.

We acknowledge our indebtedness to Dr. J. Fabricant for undertaking the virus isolation work and to John F. Garfield and Robert F. Smith, Brookhaven National Laboratory, for preparing the photomicrographs.

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FIG. 1. Pigeon exhibiting torticollis and clockwise rotation of the head. Sequence from a 16 mm. motion picture film.

FIG. 2. Leptomeningitis of forebrain. Coronal section. Hematoxylin and eosin stain. × 50.

FIG. 3. Coronal section through cerebellum and medulla. Perivascular cuffing is present in the subependymal region of the 4th ventricle and there is a spongy appearing degenerative lesion in the medulla. Hematoxylin and eosin stain. × 70.


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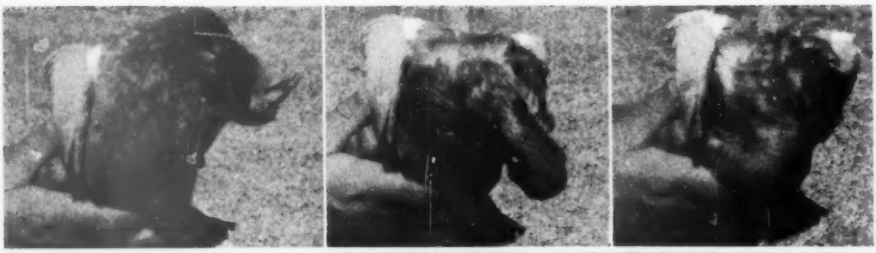

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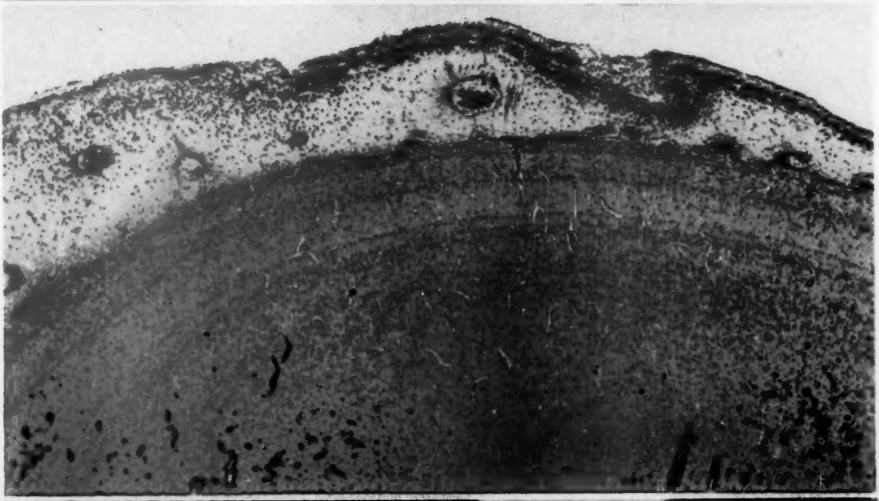

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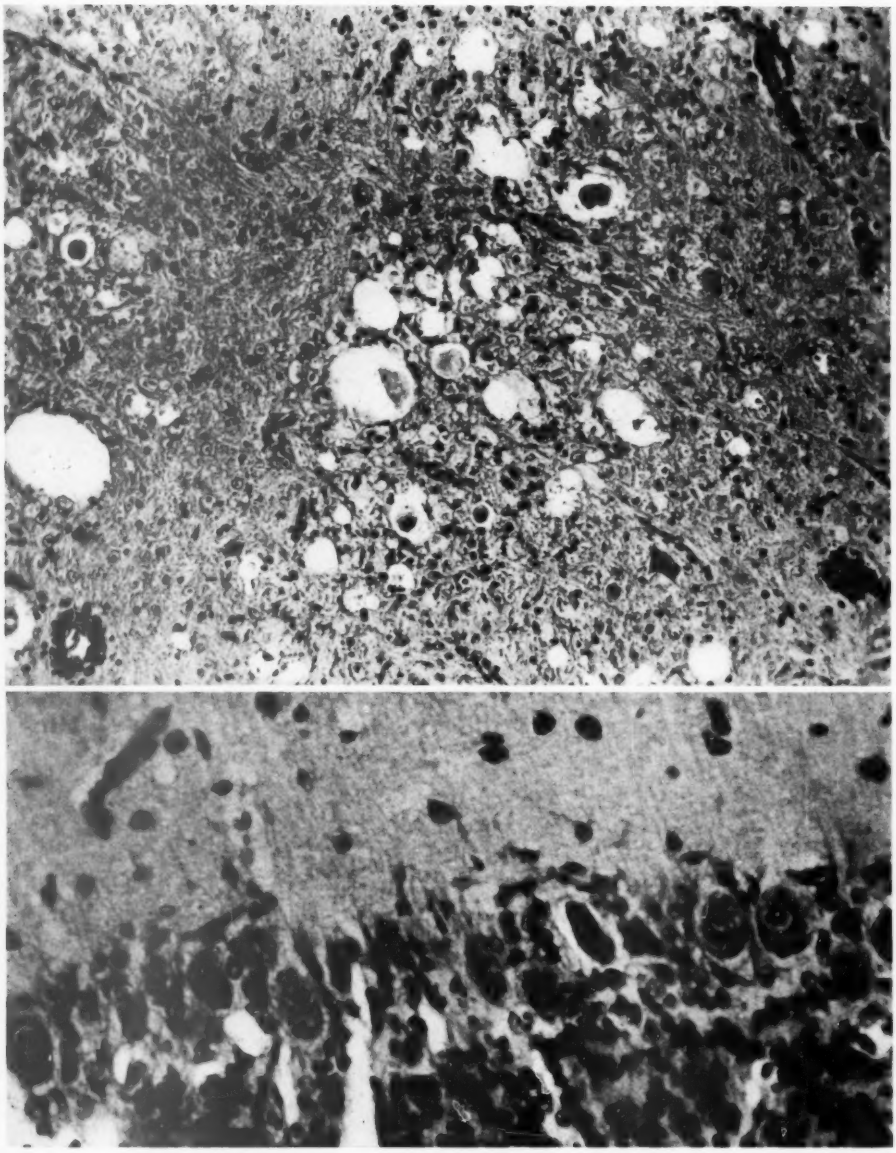
FIG. 4. Medulla oblongata with three examples of perivascular cuffs; also axonal swelling and myelin degeneration. The degenerative lesion is less extensive than the one shown in Figure 3. Hematoxylin and eosin stain. × 250.

FIG. 5. Pyknosis of some Purkinje cells with preservation of other adjacent cells. Hematoxylin and eosin stain. × 650.



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